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| Treatment of clozapine associated obesity and diabetes with exenatide in people with schizophrenia | | | | |
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**CONFIDENTIAL**

**PROTOCOL TITLE**

Treatment of clozapine associated obesity and diabetes with exenatide in people with schizophrenia

**PROTOCOL SHORT TITLE**

CODEX

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**STUDY ACKNOWLEDGMENT/CONFIDENTIALITY**

By signing this Protocol, the Investigator(s) acknowledges and agrees:

The Protocol contains all necessary details for conducting the study. The Investigator will conduct this study as detailed herein, in compliance with Good Clinical Practice and the applicable regulatory requirements, and will make every reasonable effort to complete the study within the time designated.

The Protocol and all relevant information on the drug relating to pre-clinical and prior clinical experience will be made available to all physicians, nurses and other personnel who participate in the conduct of this study. The Investigator will discuss this material with them to assure that they are fully informed regarding the drug(s) and the conduct of the study.

Except where the Principal Investigator’s signature is specifically required, it is understood that the term ‘Investigator’ as used in this Protocol and on the CRFs refers to the Principal Investigator and/or an appropriately qualified member of the staff that the Principal Investigator designates to conduct the study.

This document contains information that is privileged or confidential. As such, it may not be disclosed unless specific prior permission is granted in writing or such disclosure is required by federal or other laws or regulations. Persons to whom any of this information is to be disclosed must first be informed that the information is confidential. These restrictions on disclosure will apply equally to all future information supplied, which is indicated as privileged or confidential.

The conduct and results of this study will be kept confidential. The study Sponsor will have access to source documents entered into the Case Report Form. The results of this study may be published. Upon completion of the Study, it is the intention of the parties to prepare a joint publication regarding or describing the Study and all the results there from and both parties shall co-operate in this regard.

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List of abbreviations and definition of terms

The following abbreviations and special terms are used in this study Clinical Study Protocol.

| Abbreviation | Explanation |
| --- | --- |
| ADR  AE  BPRS-A  BD  BMI  BP  Clz  CRF  CTN  DPP-4  ELFT  FDA  GCP  GLP-1 | adverse drug reaction  adverse event  Brief Psychiatric Rating Scale - Anchored  twice daily  body mass index  blood pressure  clozapine  Case Report Form  Clinical Trial Notification  dipeptidyl peptidase-4  electrolytes and liver function test  Food and Drug Administration  good clinical practice  glucagon-like peptide-1 |
| HbA1c  HDL  HHS  HR  HREC  IB  ICH  ITT  LDL  MSAMHS  NHMRC  PD  PI  PICF  PK  PRO  QCAT  QW  SAE  SC  Scz  SU  T2DM  TG  TGA  UQ | glycosylated haemoglobin  high density lipoprotein  Hospital and Health Service  heart rate  Human Research Ethics Committee  Investigator’s Brochure  International Conference on Harmonisation  intention- to- treat  low density lipoprotein  Metro South Addiction and Mental Health Service  National Health and Medical Research Council  pharmacodynamics  Product Information  Participant Information and Consent Form  pharmacokinetics  Patient reported outcome  [Queensland Civil and Administrative Tribunal](http://www.qcat.qld.gov.au/)  once weekly  serious adverse event  subcutaneous  schizophrenia  sulfonylurea  Type II Diabetes Mellitus  triglycerides  Therapeutic Goods Administration  University of Queensland |
|  |  |

# 1. Introduction

## Background

Schizophrenia (scz) has a lifetime risk of 7.2 per 1000 persons (1). 25-50% of people with scz fail to respond to typical and atypical antipsychotics (2). For these people clozapine (clz) is the gold standard treatment (3). Life expectancy for people with scz is 16.4 years shorter than for the general population (4) with 35.1% of excess deaths attributable to cardiovascular disease and type II diabetes mellitus (T2DM)(4). Rates of lifetime prevalence of T2DM among people with scz are 14.9% (5) while metabolic syndrome prevalence rates are 32.5% (6). For people on clz, T2DM and metabolic syndrome rates are higher at 43% (7) and 51.9% (6) respectively. The mean weight gain over 10 years on clz was over 13.5kg (7).

The mechanism of action for weight gain associated with clz is not completely understood, however recent rat models suggest that clz causes acute deficits in glucose metabolism, and that the incretin hormone, glucagon-like peptide 1 (GLP-1) plays a role. GLP-1 is an intestinal epithelium produced peptide, released in response to ingestion of food. It stimulates insulin secretion and inhibits glucagon secretion, and appears to regulate appetite by inducing satiety (8). In a rat model, clz led to increased hepatic glucose output and increased glucagon levels despite high glucose levels (9). Clz does not appear to induce insulin tolerance, however it can induce a preference for high fat, high sugar foods in rats, leading to obesity (10). In obese rats, clz acutely reduced GLP-1 production (10). There is also evidence to suggest that individuals with scz are predisposed to developing T2DM, irrespective of treatment with antipsychotics (11).

There are two current incretin-based therapies designed to enhance endogenous GLP-1 action in vivo. DPP-4 inhibitors (gliptins) increase the half-life of endogenous GLP-1 by inhibiting the enzyme (DPP-4) responsible for its degradation. Incretin mimetics, such as exenatide and liraglutide, are GLP-1 analogues that mimic the effect of GLP-1 but are resistant to degradation by DPP-4. The incretin mimetics represent a recently developed therapeutic approach for treatment of T2DM, with the first GLP-1 analogue – exenatide twice daily – first approved by the FDA in 2005 followed by market authorisation of liraglutide in 2009. The long-acting formulation of exenatide administered once weekly (Bydureon) was approved in Europe in 2011 and by the TGA and FDA in 2012. Exenatide once weekly has a median half life of 2 weeks and reaches steady state concentrations in 6-7 weeks (12). Exenatide is well tolerated and does not appear to have medication interactions (13).

The actions of GLP-1 agonists are dependent on presence of a glucose load in the gut, and stimulate insulin secretion, reduce glucagon secretion, slow gastric emptying and increase satiety (8). The GLP-1 receptor agonist exenatide normalised both glucagon levels and glucose metabolism in rats given clz (10). GLP-1 agonist, liraglutide, reduced olanzapine-induced weight gain and glucose intolerance in rats (14). GLP-1 receptor agonists have additionally been shown in rat models to have an anti-psychotic like effect (15), improve cognition in rat models, enhance neurogenesis and are postulated to be neuro-protective (16).

GLP-1 agonists are TGA approved for therapeutic use in the treatment of T2DM in combination with metformin, a sulfonylurea, or a combination of metformin and a sulfonylurea. GLP-1 analogues have been shown to improve glycaemic control and reduce bodyweight in patients with T2DM (13), and have been shown to reduce bodyweight in obese people without T2DM (17). In December 2014, the FDA granted the first approval for use of a once-daily 3mg dose of liraglutide in chronic weight management in adults with obesity, or who are overweight with comorbidities. Liraglutide 3mg is currently under regulatory review in Europe and a number of other countries for use in weight management in obese or overweight adults.

The UK National Institute for Health and Clinical Excellence (NICE) guidelines suggest a GLP-1 receptor agonist as third-line therapy to first-line metformin and a second-line sulfonylurea when control of blood glucose is inadequate and where obesity is a specific problem (18). However, in treatment algorithms developed by both the American Diabetes Association/European Association for the Study of Diabetes (ADA/EASD) and the Australian Diabetes Society, GLP-1 agonists are an option for second-line and third-line therapy if glycaemic targets are not achieved with metformin or sulfonylurea monotherapy or combination therapy, particularly for patients who wish to avoid weight gain or hypoglycaemia (19, 20). The preclinical evidence showing that clozapine mediates metabolic effects by reducing GLP-1 production and that GLP-1 agonists reduce weight gain and metabolic derangements in rats treated with clozapine and olanzapine (10, 14) provides mechanistic justification that GLP-1 agonists may represent a novel approach to treatment of diabetes and obesity in clozapine-treated patients.

To date, the management of antipsychotic-induced weight gain in current clinical guidelines includes cognitive behaviour therapy interventions, dietary changes, and switching of antipsychotic medication (21, 22). However, it is not clinically appropriate for patients with treatment refractory schizophrenia to cease clozapine (the most effective medication against positive and negative symptoms) and begin a more weight-neutral but less efficacious agent. Orlistat is currently the only medication registered in Australia for use in treating overweight (with comorbidities) and obesity that has been evaluated for long-term safety (23). In accordance with current Australian obesity guidelines, it may be considered as an adjunct to lifestyle interventions in adults with BMI ≥ 30 kg/m2 or adults with BMI ≥ 27 kg/m2 and comorbidities (23). Two studies (24, 25) in clozapine-treated patients support that 16-week treatment with orlistat has beneficial effects in decreasing body weight in men (2.36-2.39 kg) but not in women. Behavioural and diet interventions also show modest effects for clozapine-associated obesity, although this is based on two small trials (26, 27) and issues of adherence and clinical resources limit the practicality of this intervention (28). Phentermine is also registered in Australia for use as a short-term (e.g. 3-month) adjunct to dietary management of obesity, under medical supervision (23). There is currently no evidence regarding the efficacy of phentermine as an intervention for antipsychotic-associated obesity. Furthermore, the evidence on the effects of these weight loss medications on health outcomes other than weight loss is limited (23). According to current Australian guidelines, unapproved medicines that are used in the treatment of other conditions and have evidence of a beneficial effect on weight (including, fluoxetine, topiramate, metformin and GLP-1 agonists) may be used when relevant comorbidities are present (23). Only two randomised controlled trials have examined the role of metformin in improving glycaemic control and reducing weight for people with scz on clz, with modest results and weight regain effects after treatment cessation (29, 30). Therefore, studies using current pharmacological and behavioural interventions for reducing clozapine-associated weight gain report only modest weight reduction, which is of substantially less magnitude than the weight gained by treatment with clozapine (28). Furthermore, the reliability of available data is limited by methodological limitations and small sample sizes. Pharmacological interventions also have adverse event profiles that limit their acceptability and these oral agents, whilst minimally invasive, may be less effective than long-acting injectable formulations in a cohort of patients with impaired cognition due to schizophrenia. Thus, to date, no intervention has the sufficient evidence needed to develop sound clinical practice guidelines for the treatment of clozapine-associated obesity. To reduce the personal, social and economic burden associated with cardiometabolic disorders that may develop secondary to weight gain, it is of significant benefit to investigate novel methods of treat clozapine-associated obesity.

To date, there have been no completed trials of GLP-1 receptor agonists in people with scz on clz. There is one case report in the literature of the successful treatment of obesity and T2DM in a woman with scz on clz (31). People with scz are known to have difficulty adhering to oral medications (32). Exenatide is available in a once weekly injectable formulation, and could be administered by clinicians, improving adherence. Therefore, in consideration of the promising preclinical and clinical data and the physiological mechanism of action, the use of a GLP-1 agonist such as exenatide, may represent a novel approach to attenuating clozapine-associated obesity and diabetes.

## Research hypothesis

**Hypothesis:** That, for people with schizophrenia on clozapine compared to controls, exenatide weekly injection will:

1. lead to improved glycaemic control (reduction of HbA1C by >0.5 percentage points) for people with poorly controlled T2DM;

2. lead to weight loss (>5%) for people with BMI>30kg/m2 without T2DM;

## Rationale for conducting this study

Schizophrenia treatments have adverse-drug-reactions (ADRs) causing increased risk of obesity, metabolic-syndrome, T2DM, cardiovascular disease and shortened lifespan. There is poor adherence to dietary and exercise advice in this population with limited metabolic improvement. Repurposing existing metabolic treatments can cost-effectively improve quality-of-life and reduce ADRs. This project translates successful treatments for T2DM to management of clozapine ADRs. Exenatide, as a weekly mental health nurse delivered injection, is practical for people with poor adherence. If this trial has positive outcomes, ADRs leading to morbidity and mortality in people with schizophrenia managed on clozapine could be reduced at a cost savings to clinical services.

## Benefit/risk

**Benefits**

This trial may have meaningful benefits for both the individuals involved and the wider healthcare system. The efficacy of once weekly exenatide in reducing HbA1c, fasting and postprandial blood glucose, and body weight as both monotherapy and in combination with first- and second-line diabetes agents has been demonstrated in the DURATION (Diabetes Therapy Utilization: Researching Changes in HbA1c, Weight and Other Factors Through Intervention with Exenatide once-weekly) trial program. The DURATION program comprised 6 randomized, comparator-controlled, 24- to 30-week trials of exenatide QW in approximately 3500 subjects with T2DM. For patients on first-line treatment with metformin, exenatide once weekly produced a clinically significant HbA1c reduction of 1.5–1.9% and was superior to exenatide twice daily, sitagliptin, pioglitazone and insulin glargine (33-37). Diabetic patients treated with exenatide QW also experienced significant reductions in body weight (-2.5 kg) after 24 to 30 weeks of treatment (38). The clinically meaningful improvements in glycaemic control and body weight have been shown to be sustained over 3 years of treatment (39). Additionally, preclinical studies have shown that exenatide can improve beta cell mass and function (40-42). This effect is of substantial clinical benefit in patients with T2DM and pre-diabetes, potentially preserving or restoring functional beta-cell mass and counteracting an underlying cause of progression of T2DM.

A growing body of data demonstrates that GLP-1-based therapies cause significant and enduring weight loss for non-diabetic overweight/obese patients as well as patients with T2DM (17). In addition to producing weight loss of 2.5-5.1kg in non-diabetic obese patients, exenatide treatment improved metabolism and glucose tolerance in the pre-diabetic state, underlining its potential in diabetes prevention for these individuals (43, 44). Furthermore, data from the large Phase 3 SCALE (Satiety and Clinical Adiposity−Liraglutide Evidence in Non-diabetic and Diabetic adults) clinical trial program consistently demonstrated that the GLP-1 analogue, liraglutide, induces and maintains weight loss and significantly improves obesity-related comorbidities and glycaemic control in obese patients (45, 46). This trial data and earlier data related to the use of liraglutide in obesity (47, 48) was pivotal in the recent submission and approval of liraglutide 3mg for weight management indications in the US.

Exenatide has shown to overcome defects in glucose metabolism caused by clozapine through normalising blood glucose and glucagon levels in clozapine-treated rats, providing population-specific evidence that exenatide may be of therapeutic benefit in these patients (10). Therefore, the potential improvements in body weight and metabolic parameters secondary to treatment with exenatide may reduce cardiovascular morbidity and mortality and improve quality of life for individuals treated with clozapine. In turn, this may translate to cost savings for clinical services and contribute to a reduced burden on health resources.

**Risks**

Exenatide weekly injection (Bydureon) ADRs are summarised in the Investigator’s Brochure. Bydureon is generally well tolerated and most side effects are transient, mild-to-moderate gastrointestinal disturbances. The most common adverse event is nausea (20%) which typically resolves 4–8 weeks after treatment initiation (49). Other common and transient gastrointestinal ADRs include diarrhoea (13%), vomiting (8%) and constipation (6%). The injection of exenatide may result in a small haematoma at the injection site and transient, regional redness or a nodule. Pruritis has been shown to develop at the injection site in 8% of patients. Nineteen percent of patients developed nasopharyngitis, 8% developed headache and 15% developed hypoglycaemia. All but one case of hypoglycaemia was classified as minor, and was more common with co-administration of a sulfonylurea. In combination with metformin, exenatide causes no increase in the incidence of hypoglycaemia due to its glucose-dependent insulinotropic mechanism. Exenatide does not impair the normal glucagon response and other counter-regulatory hormone responses to hypoglycaemia. Overall, in the absence of other diabetes medication that causes low blood sugar, hypoglycemia associated with GLP-1 agonist treatment is rare. Acute pancreatitis and acute renal failure have been reported rarely since exenatide twice daily has been marketed. There is currently no mechanism to explain this association, and cases linking exenatide to pancreatitis or renal failure are rare. Given the risks associated with exenatide, we have set exclusion criteria as listed in 4.2. Risks and distress to the subjects have also been minimized through use of the once weekly regimen. Exenatide weekly has demonstrated better tolerability and reduced gastrointestinal side effects compared to other GLP-1 agonists available as twice daily or once daily regimens (13, 33).

A standard panel of safety laboratory evaluations will be performed regularly during the trial (including vital signs, haematology, and biochemistry), and side effects will be monitored closely. Blood samples will be taken under aseptic conditions and in accordance with standard operating procedures. Subjects will not be required to attend MSAMHS clozapine clinics more frequently than what is currently required for their routine care.

# Study Objectives

## Primary objective

1. To conduct a two arm parallel open label controlled pilot trial of exenatide weekly injection (Bydureon) for patients with schizophrenia on clozapine for two separate indications:
   1. Arm A. Glycaemic control for T2DM who have inadequate glycaemic control on standard oral hypoglycaemic therapy. The primary objective is to determine the acceptability of the intervention and evaluate if 24 weeks of treatment with weekly exenatide injections cause improvement in glycaemic control, as measured by proportion of patients with reduction in HbA1c of >0.5 percentage points.
   2. Arm B. Weight loss and improved metabolic parameters for obese patients (BMI > 30 kg/m2) without T2DM. The primary objective is to determine the acceptability of the intervention and evaluate if 24 weeks of treatment with weekly exenatide injections increases the proportion of people with >5% weight loss.

## Secondary objectives

1. For Arm A - Secondary outcomes are the proportion of people with >5% weight loss, change in metabolic markers, and change in symptoms of psychosis
2. For Arm B - Secondary outcomes are change in metabolic markers, and change in symptoms of psychosis.

## Safety objective

To assess the preliminary safety and tolerability of exenatide weekly injection (Bydureon) for people with schizophrenia on clozapine.

Outcomes will be:

1. number of dropouts from the intervention arm
2. number of adverse drug reactions in intervention arm
3. scores from a structured qualitative interview with participants about their experience with study drug.

## Exploratory objectives

This research protocol is for an open label pilot study to assess acceptability, tolerability and potential effect of exenatide in people with schizophrenia for two separate indications:

* 1. Glycaemic control for T2DM who have inadequate glycaemic control on standard oral hypoglycaemic therapy
  2. Weight loss and improved metabolic parameters for obese patients (BMI > 30 kg/m2) without T2DM

If preliminary acceptability, tolerability and efficacy results are promising, future multi-centre randomised controlled trials are anticipated. As such, this pilot study aims to explore the feasibility of recruitment, randomization, retention, medication administration, assessment procedures and identify patient numbers and modifications needed in the design of larger, ensuing RCTs.

# Study plan and procedures

## Overall study design and flow chart

The present study is a 24-week investigator-initiated, two-arm parallel group, randomised, open label pilot study. The study will include 60 patients who are obese (BMI>30kg/m2) or diabetic, diagnosed with schizophrenia or schizoaffective disorder and on stable treatment with clozapine. This pilot study is designed to evaluate the acceptability of the intervention and determine the preliminary clinical efficacy and tolerability of exenatide for weight loss and glycaemic control in clozapine-associated obesity and T2DM. This study also has exploratory objectives to examine the feasibility of recruitment, retention, assessment methods and implementation of this intervention for subsequent larger scale studies.

Figure 1: Graphical study design

This will be a single-centre study carried out the Metro South Addiction and Mental Health Service (MSAMHS). Patients attending the clinics will be screened according to inclusion and exclusion criteria. Participants who meet all inclusion criteria and none of the exclusion criteria will be invited to participate in the study and the formal consent process will commence. Patients will receive detailed oral and written information about the study and written informed consent will be obtained according to the national ethical guidelines. For those who consent to participate, they will be enrolled in the study and randomized. Two subgroups of patients will be randomised: patients with T2DM (Arm A) and obese patients BMI>30kg/m2 without T2DM (Arm B). Subjects will be included in Arm A (n=30) or Arm B (n=30) according to their clinical diagnosis of T2DM or obesity (see inclusion criteria in 4.1). Participants will be randomly assigned to either the control or experimental group in a 1:1 fashion using a computer generated randomisation table. Enrolment will continue until 15 control participants in each arm and 15 exenatide treated participants in each arm have been recruited.

After subject enrolment, baseline data will be collected. After the baseline assessments, participants will be randomised to the intervention group or control group. The intervention groups will receive once-weekly subcutaneous injections with exenatide 2mg in addition to routine clinical care. Subjects in the control group will receive treatment as usual, with no changes to their normal medication regimens (treatment as usual is defined in this study is defined as 'individualized combinations of psychopharmacology, behavioural interventions, rehabilitation and associated clinical services in keeping with Queensland Health standards of care for psychosis’). The intervention period will be 24 weeks. The trial medication will be administered in the patient’s home (or in clinic if dosing coincides with routine clinic appointments) by a trained, impartial and unblinded mental health nurse. Control patients will continue to receive their routine care for the 24 week study period. In addition, all intervention participants will be referred to an endocrinologist (either A/Prof Anthony Russell, an endocrinology registrar or an endocrinology nurse practitioner) who will prescribe the study medication. Participants, investigators and healthcare staff will remain unblinded to the allocated treatment. As per MSAMHS clinic protocol, all subjects will attend the clozapine clinics at four-week intervals. Given the sensitivity of this patient group, all assessments will be made as part of routine clinical care within the MSAMHS clozapine clinic at baseline (week 0) and weeks 4, 8, 12, 16, 20 and 24. Relevant physical health measures (blood pressure, waist circumference, height, weight and BMI) will be collected by clinic nurses. Blood samples will be collected by community laboratories and analysed by Qhealth or commercial pathology services. Questionnaires and other outcome measures of interest will be assessed by a psychiatrist/psychiatry registrar during clinic consultations. After the ﬁnal dose of trial medication and on successfully completing the final clinical measures and assessments at week 24, trial participation will be terminated. All assessments and data analysis will be carried out in an unblinded fashion. The overall study design outlining outcomes measures and timeframes is presented in Table 1.

**Table 1: Schedule of Visits and Assessments**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Visit** | 0  Screening  Phase | 1  Baseline | 2 | 3 | 4 | 5 | 6 | 7 |
| **WEEK** |  | 0 | 4 | 8 | 12 | 16 | 20 | 24 |
| **SCREENING AND CONSENT** |  |  |  |  |  |  |  |  |
| Assessment of current medication | X | X | X | X | X | X | X | X |
| Informed consent | X |  |  |  |  |  |  |  |
| Medical history/concomitant illness | X |  |  |  |  |  |  |  |
| Ongoing capacity |  | X | X | X | X | X | X | X |
| Inclusion / exclusion criteria | X |  |  |  |  |  |  |  |
| Pregnancy test1 | X |  |  |  |  |  |  |  |
| Smoking | X | X | X | X | X | X | X | X |
| Retrospective chart review to assess stability of body weight in previous 3 months | X |  |  |  |  |  |  |  |
| **SAFETY** |  |  |  |  |  |  |  |  |
| Adverse events |  | X | X | X | X | X | X | X |
| Vital Signs: |  |  |  |  |  |  |  |  |
| BP | X | X | X | X | X | X | X | X |
| HR |  | X | X | X | X | X | X | X |
| Hematology2 |  | X | X | X | X | X | X | X |
| Biochemistry3 | X | X |  |  | X |  |  | X |
| Patient reported outcome questionnaire |  |  |  |  | X4 |  |  | X4 |
| Physical health assessment | X5 |  |  |  |  |  |  |  |
| **EFFICACY** |  |  |  |  |  |  |  |  |
| Body measurements: |  |  |  |  |  |  |  |  |
| Body weight | X | X | X | X | X | X | X | X |
| Height | X |  |  |  |  |  |  |  |
| Waist circumference | X | X | X | X | X | X | X | X |
| Glucose related parameters: |  |  |  |  |  |  |  |  |
| HbA1c | X6 | X |  |  | X6 |  |  | X |
| Fasting plasma glucose | X | X |  |  | X |  |  | X |
| Fasting triglycerides | X | X |  |  | X |  |  | X |
| HDL | X | X |  |  | X |  |  | X |
| BPRS-A |  | X |  |  | X |  |  | X |
| **OTHER** |  |  |  |  |  |  |  |  |
| Compliance to protocol |  |  | X | X | X | X | X | X |
| Blood clozapine/norclozapine concentration |  | X |  |  |  |  |  | X |

1. Urine pregnancy test will be performed for females of childbearing potential at screening and at any time during the trial if indicated

2. White cell count and neutrophils as per 4 weekly clozapine protocols

3. ELFTs and creatinine clearance

4. Only applicable to subjects receiving the exenatide intervention

5. The study team will liaise with clinical staff to ensure that participants have undergone a routine physical health screen

6. Only applicable to subjects in Arm A

## Rationale for study design, doses and control groups

Metabolic disturbances including glucose metabolism abnormalities, T2DM and obesity are associated with clozapine and contribute to life shortening cardiovascular morbidity. Current interventions against antipsychotic-associated metabolic dysregulation are limited and insufficient. Recent preclinical studies suggest that clozapine may mediate its metabolic effects by disruption of GLP-1 secretion (9, 10). This theory justifies the rationale that GLP-1 analogues, which have already been shown to improve glycaemic control and reduce body weight in subjects with and without T2DM, may represent effective therapeutic intervention for clozapine-associated obesity and T2DM. Despite this, no clinical trials have been completed to assess the efficacy of GLP-1 agonists in this population. Therefore, the present trial is a pilot exploratory trial with an unblinded, parallel group, randomised controlled design. The trial has been designed as a two-arm trial to investigate the potential of exenatide to induce weight loss and promote glycaemic control in two different subsets of the study population: non-diabetic obese (BMI > 30 kg/m2) subjects and subjects with T2DM. To minimize disruption and discomfort and improve recruitment rates, all participants will not be required to attend additional medical appointments outside those required for routine care.

Exenatide once weekly (QW) is a recently developed GLP-1 agonist that offers long-acting receptor agonism compared to twice daily injections of exenatide and once daily liraglutide injections. This long-acting formulation of exenatide utilises biodegradable polymeric microspheres, composed of exenatide in a matrix of poly-(D,L-lactic-co-glycolic acid) which allows for sustained steady-state plasma concentrations with a weekly injection regimen (12).

Weekly dosing with exenatide 2 mg exceeds minimally effective therapeutic plasma concentrations (~50 pg/mL) in 2 weeks with gradual increase in the average plasma exenatide concentration until steady state is reached after 6 to 7 weeks (12). Concentrations of fasting plasma glucose have been shown to improve within 2 weeks from start of treatment (33) and studies have observed progressive weight loss throughout the first 15-week treatment period (12). The PI for exenatide twice daily states that reductions in HbA1c are evident within six weeks, with most clinical benefit in glycaemic control seen within 12 weeks of commencement. Therefore, a treatment duration of 24 weeks is considered to be sufficient to determine the effects of exenatide on body weight and metabolic status. A longer trial will be considered in subsequent multi-centre RCTs as this requires larger sample sizes. Likewise, patient follow-up after stopping the treatment at 24 weeks to assess the durability of response is considered premature and is beyond budgetary constraints for this pilot study. However, this information will be valuable in subsequent RCTs once a benefit of exenatide has been demonstrated.

Given the poor adherence to hypoglycaemic regimens reported among individuals with schizophrenia (50-52) once weekly injection of exenatide offers greater practicality over other GLP-1 agonists. Johnston et al (53) reported that, over a 6-month period after initiation of GLP-1 agonist therapy in patients with T2DM, patients treated with exenatide QW had a statistically significantly greater odds of achieving adherence compared with patients treated with exenatide BD or liraglutide once daily. Correspondingly, use of exenatide QW over other GLP-1 agonists may result in improved adherence to protocol as well as minimize inconveniences and discomfort for the study population. Furthermore, in a study where 295 diabetic patients were randomized to exenatide once weekly or exenatide twice daily, the addition of either exenatide regimen to treatment with diet, exercise and/or oral glucose-lowering medication significantly improved treatment satisfaction and weight-related quality of life and this effect was maintained over the 52 week study duration (54). Greater reduction in perceived frequency of hyperglycaemia and greater treatment satisfaction was observed with once weekly exenatide compared with twice daily exenatide, suggesting greater acceptability of the once weekly regimen. Therefore, the use of exenatide once weekly in this trial may potentially offer sustained clinical effects on the patient’s quality of life during treatment

Exenatide QW has been shown to result in superior glycaemic control and better tolerability compared to exenatide BD. Studies by Drucker et al (33) and Blevins et al (55) showed exenatide QW lowered HbA1c to a greater degree than exenatide BD in patients with T2DM. Similar degrees of weight loss were noted and fewer patients experienced mild-to-moderate nausea with weekly exenatide (55). In a 26-week, randomized study comparing of exenatide QW vs. liraglutide 1.8 mg once daily in patients with T2DM, patients treated with exenatide QW had a statistically significant lower incidence of gastrointestinal tolerability problems (nausea, vomiting, diarrhoea) and lower rates of study discontinuation due to treatment-emergent adverse events (13). Both exenatide and liraglutide were found to improve glycaemic control with associated weight loss, although reductions in HbA1c and weight loss were slightly greater in the liraglutide group (13). Therefore, compared to exenatide BD and liraglutide, the use of exenatide QW offers similar glycaemic control and weight reduction while its better side effect profile enhances the acceptability of the treatment for the study population.

Patients in this study will receive a weekly exenatide 2mg SC injection for 24 weeks. No dose titration is required and only a 2mg dose form is commercially available. A dose of 2mg has been shown to have the most favourable PK and PD profile (56, 57).

This study is a randomised design where participants will be randomly assigned to either the control or experimental group in a 1:1 fashion using a computer generated randomisation table. The incorporation of a control group is a design feature to minimize bias and allow for a more realistic examination of trial acceptability and relative retention rates in intervention groups. In accordance with the NHMRC National Statement, the use of control participants with obesity who do not receive any weight loss therapy is appropriate given the genuine uncertainty as to whether currently available treatments for clozapine-associated obesity have a net clinical benefit. Control participants with diabetes also continue on their existing diabetes regimen (metformin and/or a sulfonylurea) without additional second and third line diabetes agents (including insulin, DPP-4 inhibitors, sulfonylureas and thiazolidinediones). Despite this, before study enrollment and if glycaemic control does not improve during the trial, control subjects will be fully informed about and offered these alternative treatments for diabetes, in accordance with standard practice. However, some of these agents have no established efficacy for weight loss, or are known to cause weight gain in diabetic patients. On this basis, including ‘treatment as usual’ controls is ethically appropriate given that it is in line with the usual standard practice of treating these patients in the community and it is associated with no therapeutic disadvantage for subjects and no lack of opportunity for diabetes treatment.

A placebo injection has not been incorporated into the study design given that it potentially exposes more patients from this vulnerable study population to ineffective treatments that may cause undue discomfort and distress. Employing usual-care controls instead of a blinded, placebo-controlled design for this pilot trial avoids unnecessary psychosocial harms and sources of mistrust in the therapeutic relationship. Therefore, the ethical concerns about using a placebo injection within the context of a pilot/feasibility study in vulnerable mental health patients, as well as practical considerations (budget constraints; reduction in recruitment or retention rates due the invasive nature of placebo injections) limits the feasibility of including a placebo in this pilot trial.

As the study does not use a placebo, blinding to intervention is not possible. Given that exenatide is administered by a MSAMHS mental-health nurse and also in consideration of the importance of monitoring clozapine-treated subjects to ensure clozapine’s continued safety, it is also necessary for the staff involved in the patient’s clinical care to know the treatment assignment. Therefore, trial participants, care providers, data collectors, and outcome assessors cannot ethically or practically be blinded to treatment allocation. Although assessments will be conducted in an unblinded fashion, evaluated outcomes are primarily objective (body measurements and blood analyses) and thereby lack of blinding is not likely to bias the data. There is a risk that absence of blinding of raters and patients has potential to influence subjective outcomes (the BPRS-A and medication questionnaire). However, given the extensive training and clinical experience of the raters, this risk of observer bias is unlikely to significantly affect the evaluation process. Despite this, we recognize that the lack of blinding may still limit the validity of the subjective outcomes and diminish the level of evidence provided for these outcomes. However, this is appropriate given that these are not primary outcome measures in this proof of concept trial. Should data be promising, larger placebo-controlled, blinded studies are anticipated.

We have only included patients in the age range of 18-64. This is based on the structure of the mental health service at Metro South. Patients aged 18-64 are treated in clozapine clinics managed by the psychosis and rehabilitation academic clinical units. These clinics are more amenable to recruiting trial participants. Patients aged ≥65 on clozapine are managed by the older persons academic clinical unit. The structure of these clinics make them logistically more challenging to recruit participants.

In this study, DPP-4 inhibitor (gliptin) therapy will not occur concurrently with exenatide treatment and the gliptin will be ceased for subjects in the intervention group prior to exenatide administration. Both gliptins and GLP-1 analogues are incretin-based drugs and act to potentiate the action of endogenous GLP-1 and the concurrent use of exenatide with gliptins has not been studied. However, several meta-analyses have demonstrated that, compared to treatment with a gliptin, exenatide QW produces significantly greater improvements in HbA1c and fasting plasma glucose in patients with T2DM, with no increased risk of hypoglycemia (58-61). GLP-1 analogues deliver additional therapeutic benefit of weight loss whereas gliptins are weight neutral (58, 59). Furthermore, a preclinical study by Smith et al (10) has demonstrated that the superiority of exenatide that is observed in patients with T2DM may be extrapolated to the current study population. This study used clozapine treated mouse models to demonstrate that a DPP-4 inhibitor (sitagliptin) only partially overcame clozapine-induced reduction in GLP-1 levels and did not normalise glucose tolerance, whereas exenatide normalised both glucagon levels and glucose metabolism. Therefore, the cessation of gliptin therapy in the exenatide study subjects is supported on ethical grounds by the superior glycaemic control and weight reduction benefits offered by exenatide QW.

# Subject Selection Criteria

## Inclusion criteria

For inclusion in the study subjects should fulfill the following criteria:

1. Provision of informed consent prior to any study specific procedures
2. Male or female aged 18 to 64 years
3. Clinical diagnosis of Schizophrenia or Schizoaffective Disorder
4. On oral clozapine for at least 18 weeks
5. Stable body weight (defined as less than 5kg change in weight over the past 3 months before inclusion)

For Arm A

* 1. Diagnosis of Type II Diabetes Mellitus
  2. Current and stable therapeutic doses of metformin for 3 months prior to recruitment
  3. HbA1c >7.5%
  4. BMI > 30 kg/m2 and ≤45 kg/m2

For Arm B

* + - * 1. BMI >30 kg/m2 and ≤45 kg/m2

## Exclusion criteria

Subjects should not enter the study if any of the following exclusion criteria are fulfilled:

1. Pregnancy (screened by urine human chorionic gonadotropin), lactation or no acceptance to use of effective contraception during the intervention period
2. Severe somatic disease,
   1. severe gastrointestinal disease including gastroparesis and dumping syndrome,
   2. severe renal impairment (creatinine clearance <30 mL/min) or patients with end-stage renal disease receiving dialysis
3. Allergy/hypersensitivity to exenatide
4. Hypersensitivity to excipient/s of investigational product
5. Obesity induced by other endocrinologic disorder (e.g Cushing Syndrome)
6. Participants treated with corticosteroids or other hormone therapy (except oestrogens or thyroxine) for greater than 10 days
7. Current use of any weight-lowering therapy including: pramlintide, sibutramine, orlistat, zonisamide, topiramate or phenteremine (either by prescription or as part of a clinical trial)
8. Uncontrolled hypertension (systolic blood pressure ≥ 160 mmHg and/or diastolic blood pressure ≥ 100 mmHg)
9. Previous surgical treatment of obesity
10. History of thyroid adenoma or carcinoma
11. Untreated or uncontrolled hypo/hyperthyroidism (defined as TSH >6mIU/L or <0.4mIU/L)
12. Acute or chronic pancreatitis or high risk of pancreatitis (including a past history of pancreatitis, gallstones, alcoholism and severe hypertriglyceridaemia)
13. Concurrent use of insulin
14. Any concomitant disease or condition that according to the investigator’s assessment makes the patients unsuitable for trial participation
15. For Arm B
    1. Diagnosis of Diabetes Mellitus Type I or Type II

## Rescue Criteria

Subjects will be deemed to have deteriorating glycaemic control if their week 12 HbA1c result exceeds the baseline value. These participants will be offered insulin. Subjects who commence on insulin will be discontinued from the study. Subjects who do not accept insulin may continue in the trial.

The above rescue criterion applies to all subjects except those whose SU dosage was halved at study entry (see section 5.6). For these subjects, if their HbA1c result at week 12 is greater than baseline, the SU will be maximised back to their previous dose. These subjects may continue participation in the trial.

# Study conduct

## Restrictions during the study

We have excluded the concurrent use of insulin during the study. If subjects recruited into the intervention group are using gliptins for glycaemic control, prior to first dosing of the trial product and under the supervision of an endocrinologist, the gliptin will be ceased and exenatide will be commenced as per protocol.

There are no restrictions to participants during the study in terms of diet, exercise or ambulation. Trial participants will not be commenced on other glucose modifying agents during the course of the trial. If the use of another glucose modifying agent is medically necessary for a particular participant, this participant will be exited from the trial.

Female participants will be advised not to fall pregnant during the study. Pregnancy (screened by urine human chorionic gonadotropin if indicated), lactation or no acceptance to use of effective contraception during the intervention period will be exclusion criteria.

## Subject enrollment

Study subjects will be recruited from MSAMHS clozapine clinics. Investigators will assess patients attending clozapine clinics against study inclusion/exclusion criteria. Investigators will identify potential study subjects by reviewing past medical records and diagnoses. The most recent assessments and or procedures performed as part of routine care will also be used to screen patients for eligibility. Subjects who meet all inclusion criteria and none of the exclusion criteria will be invited to participate in the study by the Investigator.

Patients who consent to participate will be enrolled into the study in either Arm A or Arm B of the study depending of their clinical diagnosis of obesity or T2DM. Baseline data will be collected and subjects will then be randomised in a 1:1 ratio into the intervention group or control group using simple randomisation. The Investigator will fully disclose to the patient the treatment they will receive as part of the study and will inform subjects of the study requirements, aims, risks and benefits. Subjects receive exenatide weekly injections or treatment as usual with clinical measures and assessments undertaken as per Table 1.

A screening log will be retained at the study site and will be utilized to track potential participants and also record the counts of individuals approached, consented, meeting inclusion/exclusion criteria, withdrawals, and completion (in keeping with standard CONSORT diagram requirements).

### Procedures for randomization

Participants will be randomised once written consent has been obtained and the baseline assessments have been completed. Participants will be randomised to one of the treatment groups, using simple randomization using a computer-generated randomization table. Participants will be randomised to the intervention (treatment with exenatide) or control group (treatment as usual) in a 1:1 ratio.

A trained, impartial and unblinded researcher will be responsible for the computer-generated randomisation list and for subsequent allocation to treatment with either exenatide or treatment as usual. The Principal Investigator will hold the randomisation list in a secure location.

Trial participants, care providers, data collectors, and outcome assessors will be unblinded to treatment assignment.

## Procedures for handling subjects incorrectly enrolledor initiated on investigational product

Any participant treated in a manner that deviates from the Protocol, or who is admitted into the study but is not qualified according to the Protocol, will be withdrawn immediately and be ineligible for analysis. The study monitor will be notified and the Investigator will undertake any follow-up action as necessary in accordance with local guidelines and regulations.

## Blinding

This is a non-blinded study. Treatment allocations will be disclosed to the Investigator, study personnel and patients.

## Treatments

### Identity of investigational product(s)

|  |  |  |
| --- | --- | --- |
| Investigational product | Dosage form and strength | Manufacturer |
| Bydureon (Exenatide Weekly Injection) | 2mg powder for subcutaneous injection vial with diluent syringe. | Astra-Zeneca |
|  |  |  |

More detailed information on the composition, storage, PK and PD of the Investigational Product is presented in the Investigator’s Brochure.

From the PI:

BYDUREON is an extended release microspheres formulation of exenatide. BYDUREON is supplied in a single dose kit containing a vial of powder, a prefilled syringe of diluent, a vial connector and two needles (one spare). BYDUREON is a sterile, white to off-white powder in a glass vial. The active ingredient in BYDUREON is exenatide. The powder is suspended using the diluent supplied. The diluent is a clear, colourless to pale yellow to pale brown solution. When the product is prepared as instructed, the resulting suspension contains 2 mg exenatide. The suspension is intended for subcutaneous use only, once per week.

Bydureon consists of exenatide (5%) and sucrose (2%) encapsulated within biodegradable polyglactin microspheres that are designed to release exenatide over an extended period of time. During dose preparation, a custom diluent is added to these microspheres, which are dispersed into the diluent to create a suspension. Following administration of the suspension, the polymer biodegrades over time, providing extended release of exenatide into the circulation. The diluent contains carmellose sodium, sodium chloride, polysorbate 20, sodium phosphate - monobasic, sodium phosphate - dibasic, and water for injections.

### Doses and treatment regimens

Intervention group members will each receive subcutaneous injections of Bydureon 2mg weekly for 24 weeks during the study period. Titration is not required. Each dose will be administered in the abdomen as a subcutaneous injection. The injection will be administered in the patient’s home or in the clinic by a trained and unblinded mental health nurse. Bydureon can be administered at any time of day irrespective of meals. Dose and dosing frequency should not be changed at any time during the treatment period. Bydureon must be injected immediately after suspension of the powder in the diluent and should only be used if the mixture is white to off white and cloudy. No trial product which has exceeded the expiry date must be used.

Control group members will receive treatment as usual. Participants will not be subject to additional tests outside those required for routine care.

### Additional study drug

There are no additional study drugs

### 5.5.4 Labeling

This is an open label study. The investigational drug will be labeled as per the manufacturer’s standard commercial label and labelling will comply with local regulatory GCP and TGA requirements and medication dispensing guidelines.

### Storage

During the shelf life, the entire kit should be stored at 2°C to 8°C. However, the kit may be kept for up to 4 weeks below 30°C during the shelf life. The investigational product will be kept refrigerated, in the original pack to protect from light, and will not be used if it has been frozen.

The study drug will be stored according to manufacturer’s guidelines at the Princess Alexandra Hospital Pharmacy. Four weeks supply of the study drug will be stored in the locked clinical medication storage room refrigerators at the Metro South Addiction and Mental Health Service outpatient clinic at 519 Kessels Rd, MacGregor, Qld, 4109. Only delegated members of the study team will have access to the investigational products.

## Concomitant and post-study treatment(s)

Details of all concomitant medication will be recorded at trial entry and any changes in concomitant medication must be recorded at each visit. If a change is due to an AE then this must be recorded and reported according to 6.4. If the change influences the subject’s eligibility to continue in the trial, then the Principal Investigator will be informed.

Concomitant use of the following compounds will not occur in the study period: insulin, any weight-lowering therapy, either by prescription or over-the-counter (including pramlintide, sibutramine, orlistat, zonisamide, topiramate or phentermine). Trial participants will not be commenced on other glucose modifying agents during the course of the trial. If the use of another glucose modifying agent is medically necessary for a particular participant, this participant will be exited from the trial.

For patients in the intervention group who are already on a sulfonylurea (SU) and have a HbA1c between 7.5% and 8.5%, the dosage of the SU will be halved to avoid hypoglycemia. For patients in the intervention group who are on a SU and have a HbA1c of >8.5% the dose of the SU will be maintained. At week 12, if HbA1c remains above the baseline value in patients whose SU dose has been halved, then the SU will be increased again to their previous dose (see rescue criteria in section 4.3).

For patients who are randomised to the exenatide group and who are already on gliptins, prior to the administration of the trial medication, the gliptin will be ceased under the supervision of an endocrinologist.

Other medications, including other anti-psychotic medications, are permitted during the study period.

There are no restrictions on medications given in the post-study period. All study participants will be recruited from MSAMHS outpatient clozapine clinics. Participation in this study will have no bearing on their ongoing treatment by MSAMHS. Patients will remain treated by MSAMHS as long as they remain open to MSAMHS.

As Bydureon is not available on PBS prescription, subjects will not be offered the investigational drug after the end of the trial. Subjects with T2DM (Arm A) meeting PBS criteria will be offered the PBS listed twice daily exenatide injection (Byetta) after the study conclusion. As Byetta is not TGA licenced for the obesity indication, subjects without T2DM (Arm B) will not be offered additional drug treatment at the end of the study. The investigator will provide counselling on future weight management and will refer the patient to multi-disciplinary health practitioners that will aid in weight management.

## Treatment compliance

The study drug will be administered by clinical nurses associated with the treating team at the patient’s home or in the clinic. Administration of the study drug will be recorded in a clinical chart and within the CRF in accordance with clinical protocols at the study site. Medication administration will be based on an assertive outreach model of care.

The Investigator will emphasise to subjects the necessity of compliance with regard to taking trial drug as described in the protocol. Refusal of the study medication, or inability to contact the study participant with repeated attempts will be recorded in the CRF. In accordance with the PI, if a dose is missed, the subject can be re-initiated on the same dose of the trial drug as soon as possible. Thereafter, patients can resume their next weekly dose on the preferred day of the week as long as it is at least one day after the last dose taken. Two injections should not be given on the same day.

It is the responsibility of the Investigator to assess the subject’s overall compliance throughout the trial and any identified issues with medication compliance will be discussed among investigators and research personnel. Subjects deemed to be noncompliant may be withdrawn at the Investigator’s discretion.

## Accountability

The Principal Investigator is ultimately responsible for the conduct of all aspects of the study and the studies compliance with GCP, National Statement on Ethical Conduct (2007), Australian Code for the Responsible Conduct of Research and local policies and procedures. If any tasks are delegated, the Investigator will record the appropriately qualified persons to whom they have specified significant trial-related duties in the Delegation Log.

The Investigator, the Hospital Pharmacist, or other personnel allowed to store and dispense Investigational Product (IP) will be responsible for ensuring that the IP used in the study is securely maintained as specified and in accordance with the applicable regulatory requirements.

All IP shall be dispensed in accordance with the Investigator's prescription. Dispensing of exenatide weekly to the clinical sites will occur once consent has been obtained and after the screening phase and randomisation has occurred. A delegated Research Pharmacist at the Princess Alexandra Hospital will dispense the trial medication. The Research Pharmacist will dispense study medication into the care of the delegated research staff, who will then sign that he/she has received the study medication. For each participant, four weeks of study medication will be dispensed and provided to CODEX delegated research staff at a time. The study medication will then be administered to the participant on a weekly basis by clinical research staff in line with this protocol (see 5.5.2). There will be a total of 24 weekly administrations of exenatide per participant.

The study drug will be kept in a securely locked area according to manufacturer’s storage requirements (see 5.5.4) and provided to the mental health nurses for administration according to the protocol. All unused kits of trial product will be returned to the study site for drug accountability.

All material supplied is for use only in this clinical study and should not be used for any other purpose. In accordance with all applicable regulatory requirements, the Investigator or designated site staff will maintain investigational product accountability records throughout the course of the study. These persons will account for and document an accurate record the amount of IP, the amount supplied, used and returned by use of an IP accountability record form. An investigational product accountability record will be kept at both the Princess Alexandra Pharmacy and the MSAMHS outpatient clinic where the trial medication will be stored (see 5.5.4) and will contain the following information:

* the date the IP was received, dispensed or returned and the identification of the participant to whom the drug was dispensed;
* the quantity of the drug dispensed for the participant
* the total balance of the IP at the site

The inventory will be available for inspection by study monitors during the study. Drug supplies from used or partially used kits will be destroyed appropriately by the research staff.

## Discontinuation of investigational product

Patients will be discontinued on the study drug by the Investigator, prior to completion of treatment, under the following conditions:

* Development of a serious adverse event assumed to be associated with the study medication
* Cessation of effective contraception, lactation or confirmed pregnancy
* Non-compliance with the study medication
* Continual inability to provide informed consent
* If the trial medication is not tolerated
* If the subject is commenced on long-term (≥10 days) corticosteroid therapy during the trial
* If the investigator suspects acute pancreatitis (all suspected drugs should be discontinued until confirmatory tests have been conducted. If tests reveal that a subject does not have acute pancreatitis, the subject can remain in the trial with re-initiation of the trial medication)
* If the Investigator determines that another glucose modifying agent is the best treatment option
* If the subject meets the rescue criteria and is commenced on insulin

Subjects in Arm B who develop T2DM during the study will not be withdrawn unless they meet rescue criteria (See 4.3). The subject should receive the best standard of care and if the Investigator determines that the best treatment option is insulin, a GLP-1 receptor agonist (e.g. exenatide twice daily injections or liraglutide once daily injections), a DPP-IV inhibitor, or other antidiabetic regimen that is not consistent with inclusion criteria, the subject must be withdrawn.

The study may be terminated prematurely by the Principal Investigator or their designee and the sponsor if:

* the number and/or severity of adverse events justify discontinuation of the study.
* new data becomes available which raises concern about the safety of the study drug, so that continuation may cause unacceptable risks to participants

### Procedures for discontinuation of a subject from investigational product

Subject withdrawal from the study and the primary reason (adverse event, noncompliance with protocol or other) for discontinuation will be recorded in the CRF. If possible, appropriate follow-up for efficacy and safety endpoints should be continued. The patient will receive the usual standard of care and withdrawal will not affect the provision of any current or future care. Subjects who are discontinued on the investigational product by the Investigator will not be replaced and will not be permitted to re-enter the study.

In case of study drug discontinuation due to an adverse event, all recording and reporting requirements for AE/SAEs will be performed as per relevant regulatory guidelines (see 6.4) and such patients will be closely monitored until the resolution or stabilization of this adverse event.

If a decision is made to terminate the study prematurely due to safety concerns, the Investigator or designee will contact all participants promptly, and written notification of study termination will be sent to the reviewing ethics committees and the relevant Governance Office. A study closure advice will also be sent to the TGA on the approved form. The clinical trial registry entry will also be updated accordingly.

## Withdrawal from study

All participants have the right to withdraw consent at any time without prejudice and this will not affect their ongoing care. This will be clearly discussed during the consenting process.

Subject withdrawal from the study will be recorded in the CRF. For cases where a participant or the legal guardian decides to withdraw consent, a form for withdrawal of participation will be completed. If possible, appropriate follow-up for efficacy and safety endpoints should be continued. The patient will receive the usual standard of care and withdrawal will not affect the provision of any current or future care.

Withdrawn subjects will not be replaced. If a participant withdraws from the study then the participant number will not be re-used nor will the participant be allowed to re-enter the study.

# Collection of study variables

## Recording of data

A Case Report Form (CRF) will be completed for each study participant to record all data directly relevant to the objectives and outcome measures detailed in this protocol. The CRF will comprise of the hard copy questionnaires, clinical assessments and measures. In the CRF, participants will only be identified by their participant ID number in order to retain participant confidentiality. The Investigator must ensure that data is recorded in the CRFs as soon as possible after visits and clinical or laboratory assessments. All CRFs should be completed in their entirety in a neat, legible manner to ensure accurate interpretation of data.

Some data may be directly entered into the CRF as source data (see 9.2.1). For any other data recorded in the CRFs, it must be possible to verify these against source documents. Recording of data in source documents other than the CRF (for example, the screening assessment form or adverse event report form) will be done and the documents will be retained in accordance with relevant guidelines.

De-identified data from the CRFs will be entered into REDCap, which is a secure (encrypted to health service standard, housed on a locally based server behind the University of Queensland firewall), web-based application for building and managing online surveys and databases. Delegated research assistants will be trained in, and responsible for, entering data into the database. The Investigator or Investigator’s authorised staff must ensure that all information derived from source documentation is consistent with the source information.

Upon completion and resolution of monitoring and data management queries, the clinical trial database will be closed. All data will be exported into SPSS software to enable statistical analysis.

The Investigator will receive the laboratory reports in paper copies directly from the laboratory involved in blood analysis. The laboratory report is retained by the site as source documentation. Relevant laboratory data will be transcribed from laboratory reports onto the CRF. The laboratory source data transcribed in the CRF must be verifiable in the source documentation.

## Data collection at enrolment and follow-up

See Table 1 for a summary of the data and clinical measures to be collected throughout the study.

### Enrollment procedures

Study subjects will be recruited from MSAMHS clozapine clinics. Prior to initiation of the recruitment phase, participating Investigators will identify potential study subjects by reviewing past medical records and the results of recent physical and laboratory based assessments undertaken as part of routine care at the clinic. The Investigator must retain a subject screening and enrolment log to record the counts of individuals approached, consented, meeting inclusion/exclusion criteria.

The Investigator or designee will complete a screening assessment document which will include the following:

* Concomitant medication
* Smoking habits
* Demographic information
* Medical and surgical history
* Concomitant illnesses
* Abnormalities noted on physical exam
* Vital signs (see section 6.4.10)
* Haematology (see section 6.4.11.1)
* Biochemistry (creatinine, HDL, fasting triglycerides; see section 6.4.11.2)
* Body measurements (see section 6.3.1)
* HbA1c (for Arm A subjects - see section 6.3.2)
* Fasting plasma glucose (see section 6.3.3)
* For females of childbearing potential: urine pregnancy test
* Results for overall eligibility

Compliance with inclusion criteria and exclusion criteria will be checked on the basis of information collected and eligible subjects will be invited to participate in the trial by the Investigator. If the subject is not eligible to continue in the trial, the subject is a screening failure and this will be recorded in the screening log.

Medical history, physical examination, laboratory, or instrumental results confirming inclusion and other screening assessment documents will be maintained in the patient’s file.

### Follow-up procedures

Once all inclusion/exclusion criteria are fulfilled, the patient becomes eligible for inclusion into the treatment. Treatment allocation will be performed as stated in section 5.2. Study medication will be delivered as stated in 5.5.2.

A number of validated clinical measures, physical health measures and information related to study safety will be collected at baseline and weeks 4, 8, 12, 16, 20 and 24. Physical measures will be conducted by mental health nurses or the psychiatrist/psychiatry registrar and blood samples will be collected by community laboratories and analyzed as per section 7. Questionnaires and other outcomes will be evaluated by the psychiatrist/psychiatry registrar during the patient’s routine clozapine clinic visits. Obtained data will be recorded in the CRF and retained as source documents. Any data collected that is also required as part of routine care or monitoring procedures for clozapine patients may be recorded in a clinical medication monitoring chart or, where relevant, registered with a clozapine patient monitoring service.

The following provides a description of the assessments to be performed and recorded in the CRF by study week:

**Baseline (week 0) visit:**

* Vital signs (see section 6.4.10)
* Body weight (see section 6.3.1.1)
* Waist circumference (see section 6.3.1.2)
* Ongoing capacity
* Concomitant medications
* Smoking status
* BPRS-A (see section 6.3.4)
* Adverse event enquiry
* Blood sampling for measurement of:
  + HbA1c (see section 6.3.2)
  + Haematology (see section 6.4.11.1)
  + Biochemistry (see section 6.4.11.2)
  + Fasting plasma glucose (see section 6.3.3)
  + Blood clozapine/norclozapine concentration

**Week 4, 8, 16 & 20 visits:**

* Vital signs (see section 6.4.10)
* Body weight (see section 6.3.1.1)
* Waist circumference (see section 6.3.1.2)
* Ongoing capacity
* Concomitant medications
* Smoking status
* Adverse event enquiry
* Compliance to protocol
* Blood sampling for measurement of:
  + Haematology (see section 6.4.11.1)

**Week 12 visit:**

* Vital signs (see section 6.4.10)
* Body weight (see section 6.3.1.1)
* Waist circumference(see section 6.3.1.2)
* Ongoing capacity
* Concomitant medications
* Smoking status
* Adverse event enquiry
* Compliance to protocol
* PRO questionnaire (see section 6.5)
* BPRS-A (see section 6.3.4)
* Blood sampling for measurement of:
  + HbA1c (for Arm A subjects - see section 6.3.2)
  + Haematology (see section 6.4.11.1)
  + Biochemistry (see section 6.4.11.2)
  + Fasting plasma glucose (see section 6.3.3)

**Week 24 visit:**

* Vital signs (see section 6.4.10)
* Body weight (see section 6.3.1.1)
* Waist circumference(see section 6.3.1.2)
* Ongoing capacity
* Concomitant medications
* Smoking status
* Adverse event enquiry
* Compliance to protocol
* PRO questionnaire (see section 6.5)
* BPRS-A (see section 6.3.4)
* Blood sampling for measurement of:
  + HbA1c (see section 6.3.2)
  + Haematology (see section 6.4.11.1)
  + Biochemistry (see section 6.4.11.2)
  + Fasting plasma glucose (see section 6.3.3)
  + Blood clozapine/norclozapine concentration

Every attempt will be made to complete the visits during the defined time period. In the cases where a visit cannot occur during the stated timeframe, any attempt at contact and reason for lost contact will be recorded on the CRF.

## Efficacy

Physical measures, clinical evaluations and laboratory assessments will be conducted at baseline and weeks 4, 8, 12, 16, 20 and 24 to assess the treatment effect. Efficacy measures include:

### Body Measurements

Body measurements will include weight, height and waist circumference.

#### Weight and Height

Weight will be recorded to the nearest 0.1 kg. Weight should be measured at screening and week 0, 4, 8, 12, 6, 20 and 24 using calibrated scales. The same pair of scales should preferably be used throughout the trial. Weight should be measured with an empty bladder, without shoes and only wearing light clothing. Weight measured at screening will only be used for the Investigator’s calculation of BMI, whereas weight measured at week 0 will be used as baseline for assessment of change in body weight.

Height without shoes will be recorded at screening.

BMI will be calculated as follows: BMI (kg/m2) = weight (kg)/height2(m2).

#### Waist Circumference

Waist circumference will be determined at screening and week 0, 4, 8, 12, 6, 20 and 24.

The waist circumference will be measured in the horizontal plane to the nearest 0.5 cm using a non-stretchable measuring tape. The subject should be standing with arms at their side and feet together. Subjects should be measured in the standing position with an empty bladder and wearing only light clothing. The observer should locate the top of the hip bone and place the tape measure evenly around the abdomen at the level of this bone. The observer should be sitting in front of the subject during the measurement. Subjects should be asked to breathe normally and the measurement should be performed end of a normal expiration. The measuring tape should lie flat against the skin without compressing the soft tissue.

### HbA1c

Samples will be drawn for all subjects at week 0 and 24 for measurement of HbA1c. HbA1c will only be assessed at screening for subjects in Arm A in order to evaluate compliance with inclusion criteria (see section 4.1).

For subjects with T2DM (Arm A), up to four measurements of HbA1c in a 12 month period will be reimbursed under Medicare Benefits Schedule. For subjects without T2DM (Arm B) quantitation of HbA1c cannot be performed more than once in a 12 month period under the Medicare Benefits Schedule. Therefore, assessment of HbA1c at week 12 will only occur for subjects in Arm A. Of the two HbA1c evaluations for subjects in Arm B (week 0 and 24), one test will be funded under Medicare while the other test will be funded privately through competitive grants.

### Fasting Plasma Glucose

Fasting plasma glucose will be assessed at screening and samples will be drawn at week 0, 12, 24 for fasting plasma glucose measurement.

### BPRS-A

The Brief Psychiatric Rating Scale-Anchored (BPRS-A; refer to Appendix B) is a widely used scale for assessing the positive, negative, and affective symptoms of individuals who have psychotic disorders. It is a brief 18-item interviewer-administered instrument that takes 20-30 minutes to complete. BPRS-A assessments will be conducted in a clinical interview to assess changes in symptoms of psychosis, rated from both observation of the patient and the patient's own report. Each item in the BPRS-A will be scored (on a 0- to 7- point scale) by patients’ treating psychiatrist/psychiatry registrar during routine consultation within MSAMHS clozapine clinics. The unblinded rater will have received trained in administering the BPRS-A and have experience with the scale. The BPRS-A will be performed at week 0, 12 and 24 and scores will be recorded in the CRF.

## Safety

The Principal Investigator is responsible for ensuring that all staff involved in the study is familiar with the content of this section.

### Definition of adverse events

An adverse event is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (eg, nausea, chest pain), signs (eg, tachycardia, enlarged liver) or the abnormal results of an investigation (eg, laboratory findings, electrocardiogram). In clinical studies, an AE can include an undesirable medical condition occurring at any time, including run-in or washout periods, even if no study treatment has been administered.

Examples of an AE include:

* Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
* New conditions detected or diagnosed after investigational product administration even though it may have been present prior to the start of the study.
* Signs, symptoms, or the clinical sequelae of a suspected interaction.
* Signs, symptoms, or the clinical sequelae of a suspected overdose of either investigational product or a concurrent medication (overdose *per se* should not be reported as an AE/SAE).
* Acute episode of psychosis

In this study, AEs may include the following documented side effects: gastrointestinal effects (nausea, diarrhoea, vomiting, dyspepsia, constipation), injection site reactions, allergic reactions.

The term AE is used to include both serious and non-serious AEs.

### Definitions of serious adverse event

A serious adverse event is an AE occurring during any study phase (ie, run-in, treatment, follow-up), that fulfils one or more of the following criteria:

* Results in death
* Is immediately life-threatening\*
* Requires in-patient hospitalization\*\* or prolongation of existing hospitalization
* Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions
* Is a congenital abnormality or birth defect

\*The term "life-threatening" in the definition of "serious" refers to an event/reaction in which the patient was at risk of death at the time of the event/reaction; it does not refer to an event/reaction which hypothetically might have caused death if it were more severe

\*\* The term “hospitalisation” is the definition of a subject admitted to a hospital/inpatient (irrespective of the duration of physical stay), or not admitted to a hospital/not inpatient, but stays at the hospital for treatment or observation for more than 24 hours. Hospitalisations for administrative, trial related and social purposes do not constitute AEs and should therefore neither be reported as AEs or SAEs. Likewise, hospital admissions for surgical procedures planned prior to trial inclusion are not considered AEs or SAEs.

Medical and scientific judgement will be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious.

In this study, psychiatric hospitalisations would be an SAE as it requires hospitalization – but this will not be reported to HREC, as this is an expected event during the course of a patient’s illness and is unlikely to be related to the investigational product.

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria above. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not a SAE. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be a SAE.

### Recording of adverse events

The investigator or delegated research staff will be responsible for the detection and documentation of events meeting the criteria and definition of an adverse event (AE) or a serious adverse event (SAE) as provided in section 6.4.1 and 6.4.2. During the study, all events meeting the definition of an AE must be collected and reported appropriately.

When an AE/SAE occurs, the investigator or delegate will review all documentation (e.g. hospital progress notes, laboratory, and diagnostic reports) relative to the event. All AEs and SAEs, either observed by the Investigator or reported by the subject, must be recorded and evaluated by the Investigator or delegate on the AE report form and the log contained within the CRF. The Investigator/institution should inform the subject when medical care is needed for adverse event(s) of which the Investigator becomes aware. If an AE changes in frequency or intensity during a study, a new entry of the event will be made in the CRF.

At each contact with the trial site (excluding visits where the subject is not seeing the Investigator or trial staff (e.g. visits to the laboratory)), the subject must be asked about AEs, and more specifically about hypoglycaemia.

From scheduled visit two onwards, participants will be asked:

*“Since your last visit, have you had any health problems?”*

*“Since your last visit have you had any episodes of sweating or shaking?”*

The following variables will be documented for each AE:

* AE diagnosis, if available.
* The date when the AE started and stopped
* Investigator causality rating against the Investigational Product (see section 6.4.3.2)
* Action taken with regard to investigational product
* Intensity (see section 6.4.3.1)
* Expectedness of the AE (see section 6.4.3.3)
* Management required for the AE (including corrective treatment/therapy given)
* Whether the AE is serious or not
* Outcome.

Adverse Events based on signs and symptoms

When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately. If no diagnosis is available then the investigator should record each sign and symptom as individual adverse events.

Adverse Events based on examinations and tests

Deterioration as compared to baseline in protocol-mandated laboratory values and vital signs should only be reported as AEs if they fulfill any of the SAE criteria or if they are medically relevant (ie. symptomatic, require corrective treatment or are the reason for discontinuation of treatment with the investigational product). Hypoglycaemic episodes (based plasma glucose concentrations or self- report) will be recorded as per section 6.4.12.1.

If deterioration in a laboratory value/vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result/vital sign will be considered as additional information. Wherever possible the reporting investigator uses the clinical, rather than the laboratory term (eg, anemia versus low hemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s).

Deterioration of a laboratory value, which is unequivocally due to disease progression, should not be reported as an AE/SAE. Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE.

#### Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study. The assessment will be based on the investigator’s clinical judgment. The intensity of each AE and SAE will be assigned to one of the following categories:

**Mild:** An event that is easily tolerated by the Participant, causing minimal discomfort and not interfering with everyday activities.

**Moderate:** An event that is sufficiently discomforting to interfere with normal everyday activities.

**Severe:** An event which is incapacitating and prevents normal everyday activities.

An AE that is assessed as severe should not be confused with an SAE. Severity is a category utilised for rating the intensity of an event; and both AEs and SAEs can be assessed as severe. An event is defined as “serious” when it meets one of the pre-defined outcomes as described in Section 6.4.2.

#### Assessment of Causality

The investigator will assess the relationship between investigational product and the occurrence of each AE/SAE. The investigator will use clinical judgment to determine the relationship. Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to the investigational product will be considered and investigated.

The causal relationship to the study product assessed by the Investigator (or medically qualified delegate) will be assessed using the following classifications:

**Not Related** In the Investigator’s opinion, there is not a causal relationship between the study product and the adverse event.

**Unlikely** The temporal association between the adverse event and study product is such that the study product is not likely to have any reasonable association with the adverse event.

**Possible** The adverse event could have been caused by the study Participant’s clinical state or the study product.

**Probable** The adverse event follows a reasonable temporal sequence from the time of study product administration, abates upon discontinuation of the study product and cannot be reasonably explained by the known characteristics of the study Participant’s clinical state.

**Definitely** The adverse event follows a reasonable temporal sequence from the time of study product administration or reappears when study product is reintroduced.

#### Assessment of Expectedness

**Expected** An adverse reaction, the nature or severity of which is consistent with the applicable product information (e.g. Investigator's Brochure for an unapproved investigational product or Product Information/package insert/summary of product characteristics for an approved product).

**Unexpected** An adverse reaction, the nature or severity of which is not consistent with information in the relevant document (e.g. Investigator's Brochure for an unapproved investigational product or Product Information/package insert/summary of product characteristics for an approved product).

#### Time period for collection of adverse events

To ensure patient safety, all AEs, regardless of suspected causality, occurring between the time of consent and until 4 weeks after the final dose of study drug will be recorded. Any SAEs experienced after this period should only be reported if the investigator suspects a causal relationship to the study drug. Each participant will be monitored regularly by the Investigator and study personnel for adverse events occurring throughout the study.

### Reporting of adverse events

All mandatory regulatory safety reporting will be reported by the Principal Investigator to the relevant regulatory authorities in accordance with local legislative requirements and ICH GCP guidelines . (62)

Expeditable events are those adverse events that are CAUSALLY related to the study product, AND that are both SERIOUS (see Section 6.4.2) and UNEXPECTED (see Section 6.4.3.3). These events are deemed Suspected Unexpected Serious Adverse Reactions (SUSAR’s). Such events are subject to expedited reporting to regulatory authorities. Reporting and reporting timeframes to the TGA and other regulators will be conducted in accordance with the relevant guidelines.

Once an Investigator becomes aware that an SAE has occurred in a study participant, he/she will immediately notify the University of Queensland (sponsor) by contacting the study monitor via telephone to notify him/her of the event. The SAE form must be completed as thoroughly as possible with all available details of the event, signed by the investigator (or appropriately qualified designee), and faxed to the study monitor within 24 hours of first becoming aware of the event. If the investigator does not have all information regarding an SAE, he/she will not wait to receive additional information before notifying the study monitor of the event and completing the form. The form will be updated with additional follow-up information as soon as available. The investigator will always provide an assessment of causality at the time of the initial report as described in Section 6.4.3.2. If data obtained after reporting indicates that the assessment of causality is incorrect, then the SAE form may be appropriately amended, signed and dated, and resubmitted to the Sponsor.

In accordance with current QH guidelines, the investigator must also notify the Reviewing Ethics Committee or site governance Office of any SAEs according the guidelines of the Ethics Committee.

All non-serious and expected adverse reactions AEs will be recorded in the CRF as per 6.4.3 and produced on request, as part of GCP.

The Principal Investigator will submit all safety updates and periodic reports to appropriate regulatory authorities, as per local requirements. The TGA will be advised of:

* any significant issue that has arisen from an analysis of overseas reports or action with respect to safetywhich has been taken by another country's regulatory agency, within 72 hours of becoming aware, and;
* Information that has an important bearing on the benefit-risk assessment of the investigational product or that would be sufficient to consider changes to the overall conduct of the clinical trial. Such information may arise as a result of monitoring of the trial, including an internal statistical analysis of data.

In accordance with applicable regulatory requirements, the Principal Investigator will also inform reviewing HREC(s), the Monitor and co-investigators of any information which may materially impact on the continued ethical acceptability of the trial or requires, or indicates the need for, a change to the trial protocol, including changed safety monitoring.

### Follow-up of adverse events

All AEs and SAEs documented at a previous visit/contact and are designated as ongoing, will be reviewed at subsequent visits/contacts and assessment will be made at each visit (or more frequently, if necessary) of any changes in severity, the interventions required to treat it, and the outcome.

For participants that have experienced AE’s and SAE’s during the trial, it will be followed-up until resolution, until the condition stabilises, until the event is otherwise explained, or until the participant is lost to follow-up. Once resolved, the appropriate AE/SAE CRF page(s) will be updated. Follow-up information (corrections, new or additional information) should be reported promptly to relevant regulators after obtaining knowledge, and if previously nonserious AEs become SAEs the CRF will be updated.

During and following a subject’s participation in a clinical trial, the Investigator will ensure that adequate medical care is provided to the subject for any adverse events, including clinically significant laboratory values related to the trial and may liaise with the treating team to optimize ongoing care as appropriate.

### Overdose

An overdose is defined as a dose taken by a patient in excess of the doses in the approved study protocol or available product information, either accidentally or intentionally, irrespective of whether it involves study medication or non-study medication. Overdose may be suspected or confirmed and may or may not be associated with clinical signs and symptoms.

It would definitely include (but not be limited to) those events which based on the investigators clinical judgment were considered to be of medical concern and /or require clinical observation and /or medical intervention. An overdose would include any dose greater than the highest daily dose included in the protocol or available product information. Deviations to study drug administration (i.e. resulting from poor patient compliance) which do not meet the definition of an overdose, will be recorded in the study medication compliance section of the Case Report Form (CRF) and not as Serious AE’s.

Signs and symptoms of overdose may include severe nausea, severe vomiting and declining blood glucose concentrations possibly requiring prolonged treatment. In the event of overdose, appropriate supportive treatment (possibly given parenterally) should be initiated according to the patient’s clinical signs and symptoms.

For all overdoses the SAE form will be completed and reported promptly to the sponsor within 24 hours and other relevant regulators in accordance with applicable guidelines. The documentation will include details of any associated signs/symptoms or if the overdose is asymptomatic, this will be stated.

### Pregnancy

Females of childbearing potential will have a urine pregnancy test performed in connection with screening visits and during the study if indicated. Details of all pregnancies in participants that occur during the treatment period and the final follow-up visit will be documented and reported to the Investigator. In addition, any pregnancies brought to the attention of the Investigator after this period, and where it is known that study medication was taken at the time of conception, will also be reported.

Although pregnancies are not generally serious AE’s, the Serious AE Form will be completed and forwarded to the Investigator within 24 hours. This will provide a record of the initial notification of the pregnancy.

Pregnancy is an exclusion criterion for this study, therefore, participants who become pregnant during the study should discontinue the study medication immediately and will be withdrawn from the study. The Investigator or delegated research staff will contact the participants treating physician and inform them of the pregnancy in writing.

### Risk Management Process

Table 2 below details the Risk Identification, Evaluation and Management plan for this study. It will ensure that risk and uncertainly are appropriately managed for the duration of the study. The risk management process is in accordance with the NHMRC National Statement on Ethical Conduct in Research Involving Humans (2007).

**Table 2: Risk Analysis Matrix**

|  |  |
| --- | --- |
| **Consequence** | **Response To Risk** |
| |  |  |  |  |  |  | | --- | --- | --- | --- | --- | --- | | **Likelihood** | **Negligi-ble** | **Minor** | **Moder-ate** | **Major** | **Extreme** | | Almost Certain |  |  |  |  |  | | Likely |  |  |  |  |  | | Possible |  |  |  |  |  | | Unlikely |  |  |  |  |  | | Rare |  |  |  |  |  | | |  |  |  | | --- | --- | --- | |  | Very High | Immediate action required | |  | High | Urgent attention or investigation required | |  | Medium | Require specific attention | |  | Low | Manage through routine procedures | |

**Risk Identification, Evaluation and Management Plan**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | Risk | Description | Possible Effects | | | Risk Management strategies |
| Likelihood | Conseque-nce | Rating |
| 1 | Psychological discomfort during interview and clinical measurements | Participants may experience psychological discomfort when answering questions in the clinical interview and when physical measurements (e.g weight, waist circumference) are taken. | Possible | Minor-moderate | Medium | The PICF clearly states the potential risk of discomfort. To reduce discomfort and disruption, all assessments will be taken as per routine care during usual clozapine clinic appointments.  Recruitment of experienced mental health clinicians who will be able to minimize and manage discomfort.  Clinicians will direct and assist participants to gain support if required. |
| 2 | Inconvenience of participating in the trial | Participants may be inconvenienced by time taken to participate in the trial. | Possible | Negligible | Low | The PICF clearly states the clinical assessments to be completed and exenatide injection regimen as well as the frequency for assessment visits. Clinical assessments will be incorporated into routine clozapine clinic visits. The once weekly exenatide formulation has been used in this study to reduce inconvenience and disruption to patients.  Participants will be given as many breaks as necessary throughout the clinical assessment visit.  Participants will be reminded that the trial is voluntary and they can withdraw at any time. |
| 3 | History of self-harm/suicidal ideation | Participant expresses suicidal ideation. | Possible | Moderate-severe | High | Recruitment of experienced mental health clinicians who are trained in conducting risk assessment and managing high risk situations.  Research staff will have access to a clinically trained senior staff including an Investigator who will assist research staff to conduct risk assessment and implement risk management plan if required i.e. notifying treating team and assisting in the participant accessing appropriate support (e.g. emergency services).  Previously identified high risk patients and recent risk assessments will be discussed at team meetings and their management reviewed by senior research staff.  Research staff will be given support and feedback on risk assessments and their management to improve skills throughout the project. |
| 4 | Blood test | Blood samples will be taken from participants according to the schedule in Table 1. Participants may experience some short term mild discomfort from the blood draw. Participants may experience minor complications such as local bruising and inflammation of the vein used. | Possible | Negligible | Low | The PICF clearly states the potential complications associated with the blood draws. Participants provide consent for this procedure which is identified on the consent form.  Trained staff will conduct the blood draws. This protocol does not require blood sampling to be done more frequently than that required as part of the patient’s routine care. |
| 5 | Overdose | An overdose would include any dose greater than the highest daily dose included in the protocol or prescribing information. | Unlikely | Minor-Moderate | Medium | For all overdoses the Serious AE Form will be completed and reported to the sponsor (as per 6.4.4) within 24 hours from the time that the Investigator or delegate was notified of the overdose.  Participants will not be provided with the trial medication for self-administration. A trained mental health nurse will administer the medication from a single dose Bydureon kit at weekly home visits.  Any identified issues with medication compliance will be discussed at weekly team meetings. Senior research staff will determine the most appropriate plan of action if required. |
| 6 | Home visits | Participants will be administered the medication in the home on nonclinic-visit weeks.  Individuals with psychosis can often experience hallucinations and delusions which could result in unpredictable behaviour. | Possible | Minor-Moderate | Medium-High | A MSAMHS protocol for home visits will be used. Trained, experienced mental health staff will conduct home visits and will carry a mobile phone. Two person visits will be conducted if clinically indicated.  Any incidents from a home visit will be reported to the Principal Investigator and documented in the CRF or if required reported to Metro South HREC. |

### Physical examination

All patients recruited in this study will be active consumers of the Metro South Addiction and Mental Health Service. The study team will liaise with clinical staff to ensure that participants have undergone a routine physical health screen.

Any abnormal, clinical significant findings at screening must be recorded as a concomitant illness. Any changes in subsequent visits as compared to screening which fulfil the criteria for an AE must be recorded as an AE (see section 6.4.1).

### Vital signs

#### Pulse and blood pressure

As per routine procedure, systolic and diastolic blood pressure will be measured preferably in sitting position at all visits to the clinic. However, re-measurement of blood pressure is allowed if white coat syndrome is suspected. Caffeine, smoking and physical activity should be avoided within 30 minutes prior to the blood pressure measurement at all visits to the clinic.

Pulse will be recorded after resting for five minutes in a sitting position at all visits to the clinic.

### Laboratory assessments

Any abnormal, clinically significant result identified at screening will be recorded as concomitant illnesses. Laboratory analysis results will be sent to the Investigator on an ongoing basis. The investigator must will report any abnormal results fulfilling the criteria for an AE according to this protocol (see section 6.4.3).

All tests required as part of routine care and monitoring for patients on clozapine will be recorded in a clinical monitoring chart and, where relevant, registered with a clozapine patient monitoring service.

#### Blood haematology

Samples will be drawn at week 0, 4, 8, 12, 16, 20 and 24 as per standard clozapine protocol, for assessment of white cell count and neutrophils. This study makes no changes to standard clozapine monitoring.

#### Blood biochemistry

Samples will be drawn at week 0, 12, 24. Assessments include: ELFTs, creatinine clearance, fasting glucose, triglycerides, HDL, LDL and total cholesterol. Creatinine clearance, fasting triglycerides and HDL will also be assessed at screening to ensure eligibility.

### Other safety assessments

#### Hypoglycaemic episodes

Based on the experience of the clinical team, inclusion of a diabetes diary or self-monitoring of blood glucose is not practical in this population. At each visit to the clozapine clinic, the patient will be asked about hypoglycaemic symptoms in a standard manner (“Have you experienced any sweats or shakes since last visit?”).Any additional plasma glucose concentrations measured by a clinician following suspicion of a hypoglycaemic episode will be recorded. Hypoglycaemic episodes will be classified according to the ADA definitions (63):

* **Severe hypoglycaemia:** An episode requiring assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions.
* **Documented symptomatic hypoglycaemia:** An episode during which typical symptoms of hypoglycaemia are accompanied by a measured plasma glucose concentration ≤ 3.9 mmol/L
* **Asymptomatic hypoglycaemia:** An episode not accompanied by typical symptoms of hypoglycamia, but with a measured plasma glucose concentration ≤ 3.9 mmol/L
* **Probable symptomatic hypoglycaemia:** An episode during which symptoms of hypoglycaemia are not accompanied by a plasma glucose determination (but that was presumably caused by a plasma glucose concentration ≤ 3.9 mmol/L
* **Relative hypoglycaemia:** An episode during which the person with diabetes reports any of the typical symptoms of hypoglycaemia, and interprets those as indicative of hypoglycaemia, but with a measured plasma glucose concentration > 3.9 mmol/L

For all plasma glucose values ≤3.9 mmol/L as well as self-reported hypoglycaemic symptoms, an AE form will be completed in the CRF to record the episode. If the hypoglycaemic episode fulfils the criteria for a serious AE, all SAE reporting and recording requirements (as per 6.4.3 & 6.4.4) will be met.

## Patient reported outcomes (PRO)

A questionnaire (see Appendix A) has been designed and implemented to measure the satisfaction and acceptability of the exenatide treatment regimen in this pilot study. This will aid in informing the feasibility of the use of exenatide weekly injections in this population for subsequent trials. This instrument consists of eight items, investigating two domains: satisfaction and usage; and adverse drug reactions. The patient’s degree of satisfaction and self-reported adverse event frequency will be rated on a 5-point Likert scale for each item, ranging from 0: “not at all” to 4: “very much”. Items are not weighted. It is anticipated that the questionnaire will be completed within approximately five minutes.

The items for the questionnaire were selected by a mental health professional on the basis of applicability and clarity. The questions relate to consumer satisfaction and perception of the overall value and acceptability of the intervention. Questions addressing satisfaction and usage and their phrasing have been modelled from validated PRO questionnaires, particularly the Treatment Satisfaction Questionnaire for Medication (version I)(64). The PRO questionnaire used in this trial will address the patient’s experience with the trial medication over the past two weeks. This timeframe has been incorporated based upon the use and reliability of this recall period in other validated PRO satisfaction questionnaires for diabetes and obesity treatments, including the Treatment Related Impact Measure–Diabetes (TRIM-D)(65), the Treatment Related Impact Measure –Weight (TRIM-Weight)(66) and Diabetes Medication Satisfaction (Diab-MedSat)(67) instruments. The descriptions chosen for the Likert scale are based on response scale used in the validated Treatment Satisfaction with Medicines Questionnaire (SATMED-Q)(68).

This PRO questionnaire will be administered by a psychiatrist/psychiatry registrar to patients who receive the exenatide intervention during the trial. It will be administered in a structured qualitative interview at weeks 12 and 24. All researchers responsible for administering the questionnaire will be appropriately trained by the Principal Investigator on how to use and score the instrument. It will be administered during the patient’s routine visit to the MSAMHS clozapine clinic. Responses will be recorded on a paper version of the questionnaire contained within the CRF (and later coded in the REDCap database).

The interviewer will explain the nature and purpose of the survey and the approximate time for completion. Patients will be asked to choose the most suitable response from the scale. Patients will be instructed that there is no right or wrong answer and to choose the response that best represents their opinion about their experience with the trial medication, whether positive or negative.

Data will be analysed to evaluate treatment satisfaction and acceptability, and identify areas where the patient’s outcome is not ideal. This will allow an assessment of how feasible this intervention will be to implement in future larger scale trials in this cohort of patients.

# Biological sampling procedures

In accordance with clozapine monitoring guidelines, patients receiving clozapine undergo blood sampling for full blood counts on a monthly basis. This study requires venous blood samples for quantification of: blood haematology (on a 4 weekly basis); HbA1c (Arm A), blood biochemistry and fasting plasma glucose (on 12 weekly basis); and HbA1c (Arm B) and blood clozapine/norclozapine concentration (at baseline and 24 weeks). Therefore, participation in this study does not require more frequent blood sampling beyond that required for routine care. Laboratory samples will be collected by a phlebotomist at a community pathology collection center as per routine standard care. Blood samples will be sent for analysis at private commercial laboratories. Assay methods, instrumentation and procedures for obtaining samples, handling and storage of samples will be conducted as per standard operating procedure of the laboratory.

Paper copies of the laboratory analysis results will be sent to the Investigator. Any abnormal, clinically significant result identified at screening will be recorded as concomitant illnesses. For any subsequent abnormal laboratory findings, the Investigator will judge if the finding is medically relevant or fulfils SAE criteria and, if appropriate, will record the value as an adverse event (see section 6.4.3). Results of laboratory tests that are required as part of the routine monitoring procedure for patients on clozapine (including white blood cell count and neutrophil blood count) may be registered with a clozapine patient monitoring service in accordance with usual clinic protocol.

The laboratory equipment may provide analyses not requested in the protocol but produced automatically in connection with the requested analyses. Such data will not be transferred to the CRF, but may be reported to the investigator according to specifications in the laboratory standard operating procedures and requirements.

## Volume of blood

The volume of blood collected during blood sampling will be in accordance with standard laboratory requirements. Approximately 4mL of blood will be drawn for the analysis of each of: HbA1c, blood counts and blood clozapine/norclozapine concentration. ELFTs, creatinine, fasting triglycerides, HDL, LDL, total cholesterol and fasting plasma glucose (or any required combination) will all be quantified from a blood sample of 5mL. During the entire study, it is anticipated that the blood to be drawn and analysed is approximately 65mL (in Arm A) or 60mL (in Arm B; due to less frequent HbA1c measurement).

# Ethical and regulatory requirements

## Ethical conduct of the study

This study will be carried out according to the Declaration of Helsinki, the NHMRC National Statement on Ethical Conduct in Research Involving Humans (2007) and the Notes for Guidance on Good Clinical Practice as adopted by the Australian Therapeutic Goods Administration (2000) (CPMP/ICH/135/95). All relevant data and records will be provided to HREC, the Monitor and regulatory authorities as required. The Investigator will take all necessary technical and organisational safety measures to prevent accidental or wrongful destruction, loss or deterioration of data. The Investigator will prevent any unauthorised access to data or any other processing of data against applicable law.

A standard panel of safety laboratory evaluations will be performed regularly during the trial (including vital signs, haematology, and biochemistry), and side effects will be monitored closely. Subjects are fully informed about possible AEs and inconveniences, and will be instructed to contact the Investigator in case of any concerns regarding the trial participation. The subjects will have the right to withdraw from the trial at any time.

Deviations from the Protocol should be avoided. Should there be questions or consideration of deviation from the Protocol, clarification will be sought from the Study Monitor and the implications of the deviation must be reviewed and discussed. Any participant treated in a manner that deviates from the Protocol, or who is admitted into the study but is not qualified according to the Protocol, will be ineligible for analysis. If an emergency occurs that requires a departure from the Protocol, the nature and reasons for the Protocol violation/deviation will be recorded in the CRF and the Principal investigator will notify the Reviewing HREC and /or Governance Office as soon as possible.

## Ethics and regulatory review

Ethics will be reviewed by the Metro South HREC and the University of Queensland Medical Research Ethics Committee**.**

Prior to submission to appointed HRECs and the Research Governance Office, the investigator will sign the protocol signature page confirming agreement to conduct the study in accordance with the protocol, GCP and other regulatory requirements locally applicable. All relevant data and records will be provided to regulatory authorities as required.

The Principal Investigator will submit the National Ethics Application Form and all associated documents including Site Specific Applications, to the appointed HREC and Research Governance Office and written approval will be obtained before participants are recruited and enrolled. A signed and dated letter that the ethics application has been approved by the appointed HREC and Research Governance Authority will be provided to the Sponsor before study initiation.

During the trial, the Investigator will promptly, in accordance with local requirements, report the following to the reviewing HREC(s): updates to IB, SAEs, substantial amendments to the protocol, non-substantial amendments according to local requirements, deviations to the protocol implemented to eliminate immediate hazards to the subjects, new information that may affect adversely the safety of the subjects or the conduct of the trial, annual progress reports of the trial status and all other documents as required by the HREC. The Principal Investigator has overall responsibility to ensure all reports are submitted in line with the appointed HREC reporting requirements.

The study will be notified under the Clinical Trial Notification (CTN) scheme and a copy of the form will be kept in the Trial Master File. The CTN form will be submitted and other reports (including reports on SAEs) to regulatory authorities according to national requirements. The trial will also be listed on the Australian and New Zealand Clinical Trials Registry.

In agreeing to the provisions of the Protocol, these responsibilities are accepted by the Investigators.

## Informed consent

Procedures of seeking and documenting informed consent will comply with the applicable regulatory requirement(s) and adhere to the ICH GCP and the requirements in the Declaration of Helsinki. A voluntary, signed and personally dated, informed consent form will be obtained prior to any trial-related interventions. The responsibility for seeking informed consent will remain with the Investigator or an adequately medically qualified person delegated by the Investigator.

Under 4.5.5 of the NHRMC National Statement on Ethical Conduct in Human Research 2007, “consent to participation in research by someone with a cognitive impairment, an intellectual disability, or a mental illness should be sought either from that person if he or she has the capacity to consent, or from the person’s guardian or any person or organisation authorised by law”. Capacity to provide informed consent, and ongoing capacity, will be assessed by the Principal Investigator who has extensive experience in assessing the capacity to consent for people with mental illness. Royal Australian and New Zealand College of Psychiatrists guidelines for assessing capacity to consent will be used and all relevant guidelines within the NHMRC National Statement will be adhered to. Ongoing capacity will also be assessed at every trial visit. Current research provides evidence that while psychotic symptoms may be present, these do not robustly predict an individual’s functionality in daily life and capacity to make decisions, and whilst strongly correlated with cognitive impairment, do not reflect an enduring inability to understand information related to research participation (69).

Under 4.5.8 of the National Statement, people with a mental illness, “consent should be witnessed by a person who has the capacity to understand the merits, risks and procedures of the research, is independent of the research team and, where possible, knows the participant and is familiar with his or her condition” (e.g. Treating Clinician). We will ensure that a witness also signs the consent form. In the event where a witness who is familiar with the patient is unavailable, an independent witness will be used for this process. A witness must be 18 years or older and must not be the Investigator, a member of the study team or their delegate.

### Adult Participants with capacity to consent

Prior to any trial-related intervention, eligible adult participants who are deemed to have capacity to provide informed consent will be given a full explanation in lay terms, with a friend or family member present if desired, of the study aims, the discomfort, risks and benefits in taking part and a copy of the relevant Participant Information Sheet Consent Form to review.

It will be pointed out to adult participants that they can withdraw from the study at any time without prejudice and it will not affect their current care. The participants will have the opportunity to ask questions. A telephone number will be provided so that participants can call a research representative who will be able to respond to any questions they may have.

Each participant will acknowledge receipt of this information by giving written informed consent for participation in the study. The consent form will be signed and dated by a witness. A notation that written informed consent has been obtained will be made on the participant’s CRF. The original, completed consent forms will be retained as source documents by the Investigator and a copy will be provided by the research staff to the participant. No study-related examinations will be conducted until the informed consent form has been signed.

In accordance with the National Statement, seeking the person’s consent will include discussion of possibility that the participant may lose capacity to consent or to participate in the research, in which case, unless contrary to the participant’s best interests, their wishes about what should happen in that circumstance should be followed. In this circumstance, the [Queensland Civil and Administrative Tribunal](http://www.qcat.qld.gov.au/) (QCAT) appointed guardian may be involved in trial-related decisions.

### Adult Participants without capacity to consent

For patients who are assessed to lack capacity for informed consent, consent will be obtained from the [Queensland Civil and Administrative Tribunal](http://www.qcat.qld.gov.au/) (QCAT) appointed guardian if such a guardian has been appointed. If no such guardian is available and the patient cannot give informed consent, they will be excluded from the study. The participant and legal guardian will be given a full explanation, in terms they can understand, of the study aims, the discomfort, risks and benefits in taking part and the legal guardian will be given a copy of the relevant Participant Information Sheet Consent Form to review.

It will be pointed out to the legal guardian that consent can be withdrawn at any time without prejudice and withdrawal will not affect current treatment. The participant and legal guardian will have the opportunity to ask questions. A telephone number will be provided so that the participant and legal guardian can call a research representative who will be able to respond to any questions they may have.

If the legal guardian withdraws consent, regardless of the continuing patient’s consent, then the patient will be withdrawn from the study. The refusal or reluctance of the participant to participate in a research project will be respected and they will be withdrawn from the study. This is to protect the person’s emotional wellbeing and continued ongoing routine care. A form for withdrawal of participation will be completed for those participants that are withdrawn from the study

The legal guardian will acknowledge receipt of this information by giving written informed consent for participation in the study. The consent forms will be signed and dated by a witness. A notation that written informed consent has been obtained will be made in the participant’s CRF. The completedconsent forms will be retained by the Investigator and a copy will be provided by the research staff to the guardian.

In accordance with the National Statement, should the participant at any time recover the capacity to consent, the Investigator will offer the participant the opportunity to continue participation or to withdraw.

## Changes to the protocol and informed consent form

Any amendments to the protocol that may affect the ethical acceptability or site suitability of the protocol will be submitted on an approved form, accompanied by all relevant updated documentation, to the appointed HREC for review and approval. Where necessary, any approved amendments by the appointed HREC will be forwarded by the Principal Investigator for submission to the Research Governance Office.

No changes to the Protocol will be implemented without prior approval from the reviewing Ethics Committee. If a Protocol amendment requires changes to the PICF, the revised Informed consent form will be approved by the reviewing Ethics Committee and site Governance Officers.

Once the final Protocol has been issued and signed by the Principal Investigator and the authorised signatories, it will not be informally altered. All protocol amendments will pass through appropriate approval steps before being implemented. Any change to the protocol constitutes an amendment.

The Principal Investigator will submit the amendment to the appointed HREC for their written approval. Completed and signed Protocol amendments will be circulated to all appointed Investigators.

Where the amendment affects the ongoing suitability of the study at a participating site, Research Governance approval will also be sought. The Research Governance Office will determine the ongoing suitability based on the amendment submitted.

The original signed copy of amendments will be kept in the Study File with the original Protocol. Where an amendment to the Protocol substantially alters the study design or if information becomes available that may be relevant to the subject’s willingness to continue participating in the trial, the Investigator will inform the subject in a timely manner, and a revised written informed consent will be obtained. Any amendments to the PICF will be reviewed and approved in advance of use.

All documents will be given a version number and date e.g. Version 1.0 15-Feb-15 to ensure that amendments to documents are tracked and verifiable and that the correct version of a document is in use according to the relevant ethical, regulatory or local approval.

Each amendment to a document will require a version number and date to be updated.

* If it is a **significant change** e.g. change in the content of the document, then the version number will be increased by 1.0.
* If it is a **minor change** e.g. contact details, then the number after the decimal point will be increased by 0.1.

# Study Management

## Training of study site personnel

The study sites will maintain a record of all personnel involved in the study including a Signature & Delegation Log which the Investigator will sign. The Principal Investigator will ensure that appropriate training is provided to study personnel to understand and comply with the provisions contained in this Protocol and that delegated staff are suitably qualified to undertake assigned tasks. The Investigator will ensure research personnel are familiar with their responsibilities in the conduct of this study, and that any new information of relevance to the performance of this study is forwarded to the staff involved in a timely manner.

## Monitoring of the study

The appointed HRECs will monitor research practice to assure adherence to the approved protocol and the NHMRC [National Statement on Ethical Conduct in Human Research](http://www.nhmrc.gov.au/publications/synopses/e72syn.htm) (2007). As part of the monitoring process, the Investigator will submit to the reviewing HREC(s), [annual (or more frequent if requested) progress reports](http://www.health.qld.gov.au/pahospital/research/gov/docs/msf17.doc), [serious adverse event reports](http://www.health.qld.gov.au/pahospital/research/gov/adverse_events.asp), [final reports](http://www.health.qld.gov.au/pahospital/research/gov/docs/msf18.doc) upon project completion and all other reports consistent with section 5.5.5 of the National Statement and Good Clinical Practice (GCP) as adopted by the TGA.

This study will be subject to a district-wide Monitoring Program implemented by Metro South HREC to ensure appropriate research conduct and consistency with regulatory requirements. Metro South HHS and UQ HREC will audit and inspect the study as required by Research Governance monitoring protocols. The Investigator will cooperate and assist with any trial-related monitoring/auditing by giving the Monitoring Officer direct access to all necessary facilities, source data and other documents relevant to the conduct of the clinical trial for review. The Principal Investigator will respond to any listed recommendations or required actions subsequent to monitoring visits, within an agreed and timely manner.

The Dr Balajo Motamari will act as the independent study Monitor. This person will conduct study documentation review to monitor the study according to GCP prior to commencement, during and after study completion and will provide the expertise and recommendations to guide the clinical trial where required. The task of the Study Monitor is to guarantee the best conduct of the study through frequent contacts by phone and in person with the responsible Investigator, in accordance with the Monitor’s Standard Operating Procedures, with the purpose of facilitating the work and fulfilling the objectives of the study. All AEs and SAEs will be reported to the Study Monitor for review. The Monitor will be given direct access to source data to review the CRFs and adverse events. The Monitor will evaluate safety data and fidelity to approved study protocol and will act as the identified person committee with suitable expertise to assist and advise HREC about reports of SAEs and other regulatory compliance responsibilities.

If an inspection of the clinical site is requested by a regulator, the investigator will inform the University of Queensland (Sponsor) immediately that this request has been received

### Source data

ICH GCP section 1.51, defines source data as "All information in original records and certified copies of original records or clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies)" (62).(62). Source documents are original documents, data and records (including hospital records, clinical and office charts, laboratory notes, pharmacy dispensing records, recorded data, copies or transcriptions, subject files, and records kept at the pharmacy, at the laboratories, and at medical departments involved in the clinical trial).

Questionnaire results and clinical assessment data is to be entered directly onto the Case Report Forms (CRF) and therefore, the CRF is considered a source document. The following data can be recorded directly on the CRFs and will be considered source data:

* PRO questionnaires
* BPRS-A
* Weight
* Height
* Waist circumference
* BMI
* Current medications
* Smoking status

Any other data that fulfils the above definitions of source data (such as laboratory results, data from adverse events and confirmation of trial participation) will also be retained in source documentation other than the CRF (such as laboratory reports, adverse event report forms and PICFs) at the study sites. For any such data transcribed into the CRF, it must be possible to verify the data against the source documents in accordance with GCP. Source documents, data and records will be retained at the trial sites to ensure that the Principal Investigator can provide direct access to the Study Monitor or regulatory authorities.

## Study timetable and end of study

The scheduled timetable of visits and assessments is reported in Table 1.

Participants allocated to the intervention group will receive the exenatide weekly injection for a period of 24 weeks. Participants are considered to have completed the study if they complete 24 weeks of dosing (intervention group) or treatment as usual (control group). After completing clinical assessments and measures at week 24, the study is considered to have ended and patients will continue to receive ongoing treatment by MSAMHS.

# Data Management

A screening log will be utilized to track potential participants and also record the counts of individuals approached, consented, meeting inclusion/exclusion criteria, withdrawals, and completion.

The Case Report Form (CRF) will comprise of the hard copy questionnaires, clinical assessments and measures. In the CRF, participants will only be identified by their participant ID number. These de-identified data will be retained in a secure room, in a locked filing cabinet, accessible only by research personnel. A copy of the PICF will be stored in a secure room in a locked filing cabinet.

Direct access to source data will be granted to authorised representatives including the Study Monitor and regulatory authorities to permit trial-related monitoring, audits and inspections.

De-identified data from the CRFs will be entered into REDCap, which is a secure (encrypted to health service standard, housed on a locally based server behind the University of Queensland firewall), web-based application for building and managing online surveys and databases. Delegated research assistants will be trained in, and responsible for, entering data into the database. A designated delegate will monitor data entered and be responsible for resolving data entry errors and discrepancies. Data quality will be ensured by performing data entry checks for consistency between the CRF and the data entry into REDCap database. These checks will be performed during data entry so that discrepancies can be resolved immediately.

Upon completion and resolution of monitoring and data management queries, the clinical trial database will be closed. All data will be exported into SPSS software to enable statistical analysis.

The Investigator must maintain confidential all study documentation, and take measures to prevent accidental or premature destruction of these documents. The patient's personal data shall be treated in compliance with all applicable laws and regulations and appropriate measures will be taken to assure confidentiality of subject data and protect the identity of human subjects in all presentations and publications.

The Investigator or their delegate will organise the retention of documentation relating to the study (source documents, informed consent forms, approvals) for a period of at least 15 years or the time frame as determined by local regulations, whichever is the longest.

# statistical Methods and sample size determination

## Description of analysis sets

### Efficacy analysis set

Efficacy will be assessed according to standard Intention to Treat (ITT) analytic procedures. This will consist of all allocated patients, irrespective of the patient’s compliance with the study protocol. Per protocol analysis will also be reported. For those who do not complete the 24 week study period, we will carry forward their last observation on the study outcomes. For all efficacy analyses, patients will be included in the treatment group to which they were originally randomised to.

For all weight and glycaemic efficacy endpoints, only observations prior to rescue medication will be included in the statistical analyses and summaries, as rescue medication will confound the subsequent measurement of these parameters. Excluded observations will be listed.

### Safety analysis set

Safety analyses will be conducted on all allocated subjects who have been exposed to at least one dose of trial product. Subjects in the safety analysis set will be analysed per protocol.

Laboratory safety parameters are measured throughout the trials and comprise haematology and, biochemistry as defined in the flowchart. No formal statistical analyses are planned for the laboratory safety parameters.

## Methods of statistical analyses

Data will be analysed as changes from baseline to follow-up for all participants and for the exenatide and control arms separately.

Continuous data will be presented by descriptive statistics with the number of observations, mean, median, standard deviation, range (minimum and maximum), as well as number of missing data (if relevant). Summary statistics for categorical endpoints will include number of observations, counts, percentages and number of missing data (if relevant). Baseline data are defined as the last measurement performed before the first study drug intake.

Comparison of data between intervention and control groups will be analysed using independent sample t-tests (for continuous outcomes) & chi-square tests (for categorical data) from baseline to last observation end-point. We will also compare change in scores using paired t-tests (continuous) & McNemar tests (categorical data).

Last observation-carried forward methods will be applied to handle missing data; no other attempt will be made to impute missing values and only observed values will be used in data analyses and presentations.

In the event that relevant baseline demographic, illness or treatment parameters differ signiﬁcantly between the two groups, these parameters will be included in a multivariate logistic regression analysis model. Multivariable linear regression analysis may be performed to study the correlation between outcome parameters and baseline patient characteristics.

The p value significance level will be set at <0.05. All data will be analysed using SPSS software.

Any deviations from the original statistical plan will be described and justified in an amended protocol and/or in the final report, as appropriate

### Interim analyses

Interim analysis is not planned for this study.

## Determination of sample size

Due to the preliminary nature of the trial (a pilot study), the planned sample size is based on the pragmatics of recruitment and patient flow and the necessities for examining feasibility, along with limitations of the funding. There are approximately 520 patients attending clozapine clinics at MSAMHS. Preliminary data from the Investigator’s clinic indicates that approximately 10% of clinic attenders will have inadequately controlled T2DM while approximately 70% of clinic attenders are obese (BMI >30 kg/m2). Based on prior experience, a 30% study refusal rate is anticipated. Therefore, we plan to randomise a total of 60 subjects to the study with 30 patients in both Arm A and Arm B. Patients will be evenly distributed between intervention groups (n=15) and control groups (n=15) in both arms of the trial. Data from this pilot study, including dropout rates, will be used to inform power calculations for subsequent larger scale RCTs.

# Investigator Indemnification

The clinical trial insurance may reimburse participants for costs of medical care that occur as a result of complications directly related to participation in this study. The Investigator and insurance company (UQ’s Clinical Trial Protection) will be notified as soon as possible if this occurs or where a causal relationship cannot be excluded. All SAE’s will be reported to the nominated insurance company.

The University of Queensland (Sponsor) will enter into a liability insurance policy agreement that covers the liability of the Investigator. This insurance policy is in accordance with local laws and requirements.

# Publication Policy

Results will be disseminated by peer reviewed publications and scientific conference presentations. Manuscripts will be prepared for publication in scientiﬁc journals in accordance with the CONSORT 2010 Statement.

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# Appendix

APPENDIX A

**Patient Reported Outcome Questionnaire**

**PATIENT REPORTED OUTCOME QUESTIONNAIRE**

Patient ID: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ Date:\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

Visit (circle one): Week 12 Week 24

Medical condition for which the subject is receiving the medication (circle): diabetes / obesity

Rate items 1–8 on the basis of the individual's self-report. Please cross the response that best describes the how the subject has felt about the study medication over the **PAST TWO WEEKS**.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Satisfaction and Usage**  *Over the past two weeks…* | | | | | |
|  | **Not at all** | **A little bit** | **Some-what** | **Quite a bit** | **Very much** |
| 1. How satisfied have you been with exenatide? | 🄋 | ➀ | ➁ | ➂ | ➃ |
| 2. For this question, choose ONE of the options below as applicable to the subject  *For subjects* ***with*** *diabetes:* How satisfied have you been that that exenatide helps to control sugars?  *For subjects* ***without*** *diabetes:* How satisfied have you been that that exenatide helps to reduce weight? | 🄋 | ➀ | ➁ | ➂ | ➃ |
| 3. How satisfied have you been with the method of medication delivery? | 🄋 | ➀ | ➁ | ➂ | ➃ |

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| *Based on your experience with the study medication over the past two weeks…* | | | | | |
|  | **Not at all** | **A little bit** | **Some-what** | **Quite a bit** | **Very much** |
| 4. Would you be prepared to use this medication in the future, if it became available? | 🄋 | ➀ | ➁ | ➂ | ➃ |
| 5. How confident are you that you could administer exenatide to yourself? | 🄋 | ➀ | ➁ | ➂ | ➃ |
| 6. Would you be prepared to administer exenatide to yourself rather than have a nurse do it for you? | 🄋 | ➀ | ➁ | ➂ | ➃ |

**Adverse Drug Reactions**

|  | **Not at all** | **A little bit** | **Some-what** | **Quite a bit** | **Very much** |
| --- | --- | --- | --- | --- | --- |
| 7. *Over the past two weeks, how bothered have you been by any…* |  |  |  |  |  |
| a. Nausea | 🄋 | ➀ | ➁ | ➂ | ➃ |
| b. Vomiting | 🄋 | ➀ | ➁ | ➂ | ➃ |
| c. Dizziness | 🄋 | ➀ | ➁ | ➂ | ➃ |
| d. Diarrhoea | 🄋 | ➀ | ➁ | ➂ | ➃ |
| e. Constipation | 🄋 | ➀ | ➁ | ➂ | ➃ |
| f. Headache | 🄋 | ➀ | ➁ | ➂ | ➃ |
| g. Sore throat | 🄋 | ➀ | ➁ | ➂ | ➃ |
| h. Reflux | 🄋 | ➀ | ➁ | ➂ | ➃ |
| i. Abdominal discomfort | 🄋 | ➀ | ➁ | ➂ | ➃ |
| 8. *In the last two weeks, have you noticed any:* |  |  |  |  |  |
| a. Injection site itchiness | 🄋 | ➀ | ➁ | ➂ | ➃ |
| b. Injection site redness | 🄋 | ➀ | ➁ | ➂ | ➃ |
| c. Injection site pain | 🄋 | ➀ | ➁ | ➂ | ➃ |
| d. Injection site bumps | 🄋 | ➀ | ➁ | ➂ | ➃ |

Do you have any other comments about your feeling towards exenatide, or about how your wellbeing has been affected by your exenatide treatment?

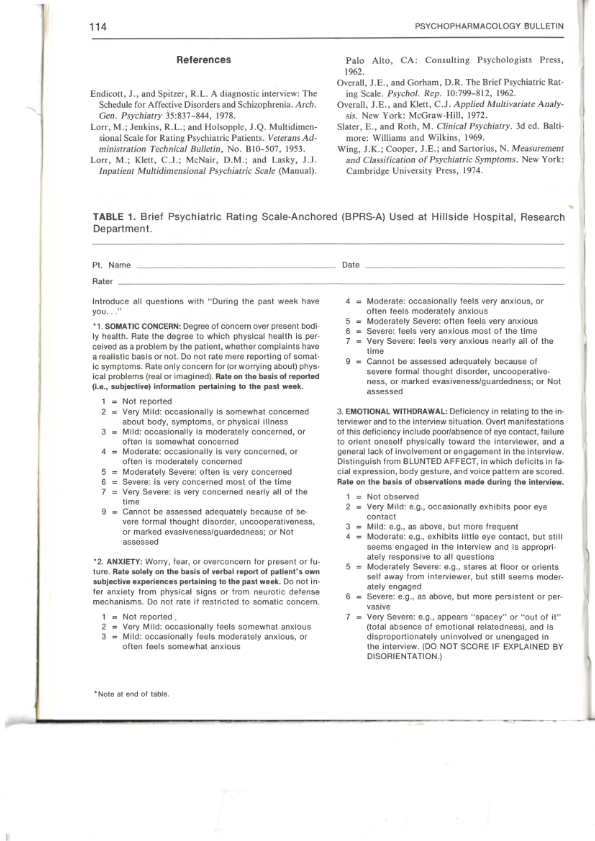
APPENDIX B

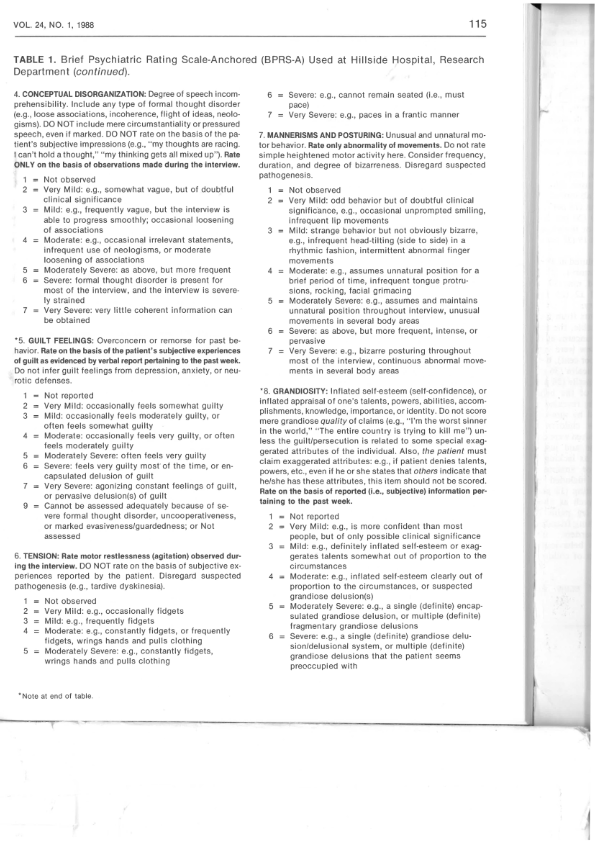
**The Brief Psychiatric Rating Scale-Anchored**

Patient ID: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ Date:\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

Rater: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

Visit (circle one): Baseline Week 12 Week 24

****Medical condition for which the subject is receiving the medication (circle): diabetes / obesity

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